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ORGANIC COMPLEXES FROM ALBERTA BENTONITES—
—THEIR UTILITY AS MEDICAMENT CARRIERS

by

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A THESIS

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The undersigned hereby certify that they have read and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Organic Complexes from Alberta Bentonites—
—Their Utility as Medicament Carriers", submitted by Cheu-fen Tsai in partial fulfilment of the requirements for the degree of Master of Science.

ABSTRACT

Bentonite samples were obtained from selected Alberta deposits. The clays were purified by water sedimentation and then subjected to physical tests. Rheograms of aqueous magmas were plotted for each of the purified clays to illustrate inherent differences in consistencies among the clays.

Each of the purified samples was reacted with a commercially available mixed quaternary ammonium salt to form an organo-bentonite complex. These complexes differed from the original clay in that the lattice spacings were expanded, as shown by x-ray diffraction data. Each possessed outstanding swelling and gelling characteristics when dispersed in a mineral oil-alcohol medium. Consistency data for these dispersions could not be related to similar data obtained for the corresponding bentonites.

From a selected number of these complexes, excellent emulsified lotion bases were prepared. Both anhydrous and emulsion type ointment bases were also formulated. In general, all of the bases studied showed an acceptable range of compatibility when shelf tested as medicament carriers.

A limiting factor in the use of these bases in dermatological formulation was the development of undesirable color with such medicaments as tannic and salicylic acids. This phenomenon was attributed to the presence of significant amounts of iron in the clays.

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INTRODUCTION

The affinity of clay components for certain organic compounds has been noted and used in different fields for many years. The decolorization of crude petroleum (1), the precipitation of alkaloids from aqueous extractions (2) and the fixation of humic acid and protein (3) are only a few of the uses to be found in the early literature. Prior to the early 1930's, the exact nature of the fundamental constituents of clays was still unknown. There was no precise concept of the reaction between the clay and organic compounds and the nature of clay-organic complexes. However, the finding that clay materials were composed of small crystalline particles and the determination of the structure of the particle provided a new basis for such studies. Since then a large number of reports dealing with these phenomena have been published and as a result the character of clay mineral-organic reactions has been fairly well established.

Several types of reactions have been studied in the past. Among these were:

- (a) color changes due to an acid-base or oxidation-reduction mechanism,
- (b) chemical formation of covalent bonds between silicon atoms and organic radicals,
- (c) displacement of adsorbed water on the clay lamellae by non-ionic polar molecules,
- (d) exchange adsorption of organic anions on the positive

edges of the clay units, and

- (e) exchange adsorption of organic cations on the negative surface of the clay units.

OCCURRENCE, STRUCTURE AND PROPERTIES OF BENTONITE

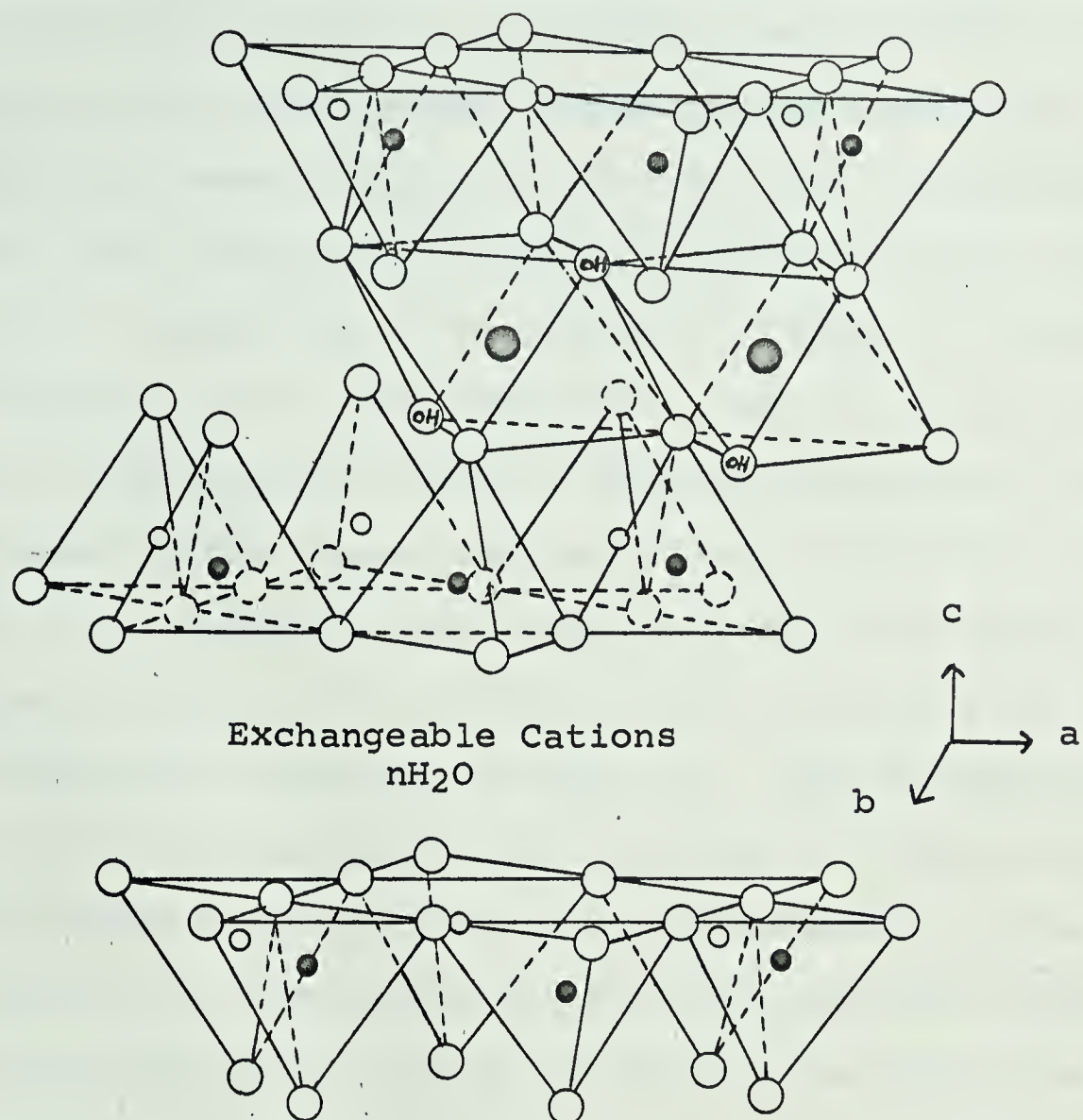
Bentonite is a native colloidal hydrated aluminum silicate. The official grade is available as a fine, odorless, pale buff or cream-colored powder. It possesses a slight earthy taste and is free from grit (4). However, the crude sample is usually colored from white to cream, gray, pink, brown or even black depending on the nature of impurities which chance to be present (5).

Bentonite is defined as a "transported stratified clay formed by the alteration of volcanic ash shortly after deposition" (6), but use of the term is often extended to include material of primarily a montmorillonite composition which may have formed in another manner (7). It is generally agreed that bentonite is a rock term used to designate a naturally occurring, very fine-grained material largely composed of the clay mineral montmorillonite. The remainder is made up of varying amounts of non-clay materials such as quartz, feldspar, etc. Bentonites are widely distributed in the Tertiary and Upper Cretaceous ages (8), as in the Midwest of the United States and in Canada. Of the many available varieties of bentonite, that produced in the Black Hills region of Wyoming and South Dakota is reported to be of the highest quality for pharmaceutical

purposes (9) .

Under the electron microscope, the bentonite particles are found to be shaped as flat plates. They are usually in the order of 0.5 to 2.5 microns in size (10) . Length of the flakes is from 10 to 100 times the thickness. One cubic inch of bentonite is estimated to contain 9,500 billion particles with a total surface area of more than one acre. When bentonite is used as an emulsifier, the clay flakes form a thin film at the oil-water interface and the large surface area of the particles aids in the entrapment of the oily globules as they are broken down by mechanical agitation (11) .

According to Hofmann et al. (12) , montmorillonite is built up of layer units made up of two silica tetrahedral sheets with a central alumina octahedral sheet. The two outer layers of silica tetrahedra are tied together at three corners to form an outer hexagonal net of oxygen atoms. The inward-pointing apical oxygens of tetrahedra together with co-planar hydroxyl ions surround an inner layer of octahedrally co-ordinated aluminum ions. The layers are continuous in the a and b directions and are stacked one above the other in the c direction (Fig.1) . In the stacking of the silica-alumina-silica units, oxygen layers of each unit are adjacent to oxygen layers of the neighbouring units with the consequence that there is a very weak bonding between the layers. Water or certain polar organic molecules can penetrate between the unit layers, causing the lattice to expand.



○ Oxygens ⊙ Hydroxyls ● Aluminum, iron, magnesium
○ and ● Silicon, occasionally aluminum

Fig.1. Diagrammatic Sketch of the Structure of Montmorillonite*

*Taken from Grim, R. E., Clay Mineralogy, McGraw-Hill Book, Co., Inc., New York, 1956, p. 56

Montmorillonite always has some degree of isomorphous substitution of Mg^{++} or Fe^{++} for Al^{+++} in the octahedral sheets, and Al^{+++} for Si^{++++} in the tetrahedral sheets, thus creating a net negative charge which is satisfied by exchangeable cations held largely on the basal oxygen surface of the tetrahedral layer. The most common cations are Na^+ and Ca^{++} , whereas Mg^{++} and H^+ occur less frequently. Under suitable conditions, the cations may be replaced by other ions (13). This is referred to as "base exchange" or "cation exchange". Under a given set of conditions, various cations were not equally replaceable and the replacing power of the common ions was found, according to Way (14), to be in the order of $Na < K < Ca < Mg < NH_4$. The cation exchange capacity (C.E.C.) of montmorillonite is usually 70 to 110 milli-equivalents per 100 grams of clay (7). Approximately 80 per cent of the exchange positions of montmorillonite are claimed to be on the basal plane surfaces with the remainder on the edges of the flakes (15). The surface area of one exchange position for a montmorillonite with C.E.C. of 100 meq. per 100 grams of clay is estimated to be 165 \AA^2 (16).

Bentonite is insoluble in water and organic solvents but it develops plasticity when mixed with a limited amount of water. It will adsorb from eight to fourteen times its volume of water (17) and produce a gel resembling petrolatum jelly. When aqueous suspensions containing three to seven per cent of bentonite are prepared, the clay swells rapidly in the water to form a thick, gelatinous system. To explain this phenomenon, Wherry (18) pointed out that the particles of bentonite were of

colloidal dimension: That is, they were of less than microscopic thickness but of microscopic breadth. This would account for their extreme swelling when moistened because their micaceous texture would permit penetration of water molecules between the constituent plates.

The aqueous dispersion of bentonite is slightly alkaline due to the hydrolysis of sodium silicate. As suggested by Barr and Guth (19), the reaction could be presented as follows:



Since silicic acid is weakly ionized, the highly ionized sodium hydroxide would give a pH 8.5 to 10 in a two per cent dispersion. The pH of bentonite dispersion does not change appreciably on standing (19).

By means of electrometric titrations, Slabaugh and Culbertson (20) found that electrolyzed acid bentonite exhibited diprotic character. They proposed that the hydrogen ions in the more accessible positions were neutralized first. This would include those on the edges and exposed layers of the clay laminae.

La Rocca and Burlage (21) demonstrated that the pH of the outer phase had a marked effect on the stability of bentonite suspensions which were more stable in neutral and alkaline than in acid medium. In the latter case, the metallic ions on the montmorillonite plates were exchanged for hydrogen ions with a concurrent loss in swelling properties (19, 22). For this reason, bentonite was not readily maintained in acid media.

It was observed that bentonite magmas exhibit the phenom-

enon of thixotropy (23). The word "thixotropy" means to change by touch; it refers to an isothermal gel-sol-gel transformation characterized by a breakdown of structure with agitation and followed by the reformation of a rigid structure when the material is allowed to stand undisturbed for some time. Thixotropy is the result of an internal structure so constituted that when broken down it can rebuild itself, if not prevented from doing so by externally applied forces (24). The formation of a thixotropic gelatinous structure in a bentonite magma was visualized as an association of a loose network of the clay particles interconnected at only a few points on the flakes (25, 26, 27, 28). The ultramicroscope studies of aqueous bentonite gels by Hauser and Reed (29) indicated the formation of primary clusters of individual particles followed by secondary aggregation of these clusters into a network intermeshed with channels and patches of dispersing medium. From light-scattering studies, McEwan and Pratt (30) concluded that there was an edge-to-edge association of particles forming flat ribbons. However, van Olphen (27, 31, 32) pointed out that the electrical and van der Waals interactions between the positive edges (due to the disruption of the octahedral alumina sheets) and the negative faces (due to the isomorphous substitution) formed an edge-to-face and edge-to-edge card-house structure. The reduction of the viscosity by stirring indicated that shear caused a breakdown of the particles linked in the skeleton structure of the flocculated system. The restoration indicated that during a period of rest, the links were re-established when Brownian

motion brought the particles back together.

The low-particle size bentonite dispersion also exhibited a rheopectic phenomenon under suitable conditions. Here the restoration of the original consistency of the stirred sol was accelerated by applying low shear rates, e.g., by gently tapping the vessel.

This was considered to be due to the increased collision frequency resulting in more chances for the structure to re-establish itself (25, 26) .

Levy (33) investigated the thixotropic properties of montmorillonite dispersions. His experimental data showed that there were significant changes in rheological properties of the dispersions on aging.

Slabaugh, Williams, Nash and their co-workers (20, 34, 35) have demonstrated that the type, the amount and the ratio of exchangeable cations on the bentonites, and the nature and concentrations of electrolytes in the dispersing medium play a decisive role in determining the rheological structure and the stability of the bentonite-water system. Foster (36) found that the degree of swelling of sodium montmorillonite was not correlated with C.E.C. or with charge on the tetrahedral layer, but was related to the octahedral substitution. There was an increase in swelling with increase in octahedral substitution.

REACTIONS BETWEEN ORGANIC COMPOUNDS AND BENTONITE

A. Non-ionic Polar Molecules

Bradley (37) and MacEwan (38, 39) first showed that a large variety of polar organic molecules, e.g., mono- and polyhydric alcohols, ethers, aromatic hydrocarbons, aldehydes, ketones, nitro-compounds and nitriles, could be adsorbed on the basal surface of montmorillonite. The molecules entered between the montmorillonite laminae and caused an expansion along the c-axis, which could be followed by x-ray diffraction techniques. The finding of a definite and sharp basal reflexion line at 17.7° Å for montmorillonite-glycol complexes by MacEwan gave a simple and reliable method for identification of the clay mineral. This method eliminated the great difficulty previously encountered due to variation of the basal spacings according to the state of hydration.

From the obtained data, both Bradley and MacEwan concluded that the polar molecules were held to the clay surface through a $\text{CH}\cdots\cdots\text{O}$ bonding and the organic molecules were orientated in a position as flat as possible. These adsorbed molecules were playing essentially the same role as water in the "hydrate" of montmorillonite.

Hoffmann and Brindley studied the adsorption of nitriles, ketones, esters, ethers and alcohols and concluded that the amount of adsorption on montmorillonite was determined by the size and chemical character of the molecule in question (40).

B. Organic Cations

Early in 1933, Giesecking noted that a number of large colored cations were strongly adsorbed by the clay and that clays saturated with these cations no longer associated with water to form gels (41). The first systematic study of the exchange reaction of organic bases and their salts with bentonite was done by Smith (42) who gave the adsorption isotherms for salts of some alkaloids and amines, and presented evidence that the reaction was one of base exchange. Giesecking (43) studied the replacement of the Ca^{++} and H^+ on montmorillonite by various substituted ammonium ions and found that the replacing cations were located between the layers and adsorbed very strongly by the clay. These ions could be exchanged by other cations of approximately the same size but not by small ions. The large organic cations adsorbed on the clay laminae gave rise to greater basal spacing than those saturated with small ions. The gradual increase in the amount of cation added resulted in a continual increase in basal spacing until a maximum was reached. Hendricks (44) showed that relatively small organic cations could cover all of the exchange positions, as did inorganic cations. On the other hand, flat organic ions, such as brucine or codeine, when adsorbed on the basal surface of montmorillonite might be of sufficient size to blanket more than one exchange position and might therefore neutralize less of the hydrogen on the acid clay ("cover-up" effect). He also suggested that the organic cations were held not only by Coulomb

forces between the ions but also by van der Waals attraction of the molecules on the clay surface, and that the organic ions were oriented between the layers so as to cause minimum expansion.

Grim (45) and Cowan (46) with their co-workers noted that organic cations in amounts less than equivalent to the cation exchange capacity of the clay were rather completely adsorbed. These ions were adsorbed on the clay laminae through exchange mechanism. However, for large substituted ammonium ions, the adsorption of about 2.5 times the C.E.C. of the clay was observed. The excess amounts of organic ions were thought to be adsorbed physically by van der Waals forces on the exchange-adsorbed cations (45).

Slabaugh (47) measured the free energy and entropy changes of adsorption of large ammonium ions on montmorillonite and stated that when an amine ion exchanged with sodium ion on the clay in an aqueous medium, at least four factors were concerned:

- a) dissociation of the sodium ion from the clay laminae,
- b) association of the amine ion onto the surface of the clay particles,
- c) orientation of the amine ion around the exchange sites, and
- d) adsorption of the hydrocarbon chains of the amine onto the clay surface accompanied by the removal of water which was previously adsorbed on this surface.

From the Fourier transform data of certain organic ammonium-bentonites, McAtee (48) concluded that the clay tended to complex

the organic material in a fairly regular and stepwise manner. He also pointed out (49) that the organic ammonium ions on the montmorillonite could be exchanged by other organic cations. The amount of exchange was proportional to the basicity of the exchanging compound and inversely proportional to the size. The replacement of large organic cations on clay by an inorganic ion did indeed take place although the amount was small.

The equilibrium constant measured by Slabaugh and Kupka (50) showed that the affinity of the substituted ammonium cations to montmorillonite increased with the increasing number of carbon atoms -- because of an increase in van der Waals forces.

PROPERTIES OF ALKYLAMMONIUM BENTONITES

A. Hydrophobic and Organophilic

Giesecking (43) first pointed out that montmorillonite saturated with large substituted ammonium ions did not show the water absorption, swelling and dispersion characteristics of Calcium, Sodium, and Hydrogen montmorillonites. Later Grim, Allaway and Cuthbert (45) showed that the ability of the clays to absorb water was greatly reduced by treatment with organic cations and the water contents of the treated clays were lower than that of untreated ones. According to Hendricks (44) the decrease of water adsorption was due to: a) the large volumes of the cations employed which excluded water from large areas of the surfaces concerned, and b) the destruction of the hexagonal network structure of the water molecules (15) on the

remainder of the clay surface.

Hauser (51) further discovered that certain organic bentonites had the property of swelling and dispersing in organic liquids. This organophilic property was believed due to the coverage of hydrocarbon chains on the clay laminae as proposed by Jordan (52) who pointed out that when organic molecules were adsorbed by montmorillonite through base exchange reaction, the molecules tended to be attached more or less in their entirety onto the surface of the mineral plates. In the meantime, the hydrocarbon portions attached themselves to the clay surfaces through adsorptive forces and displaced the previously-adsorbed water molecules. Consequently the surface of the exchange complex was no longer wetted by water and became preferentially wetted by oil. Thus, a bentonite originally exhibiting high swelling in water, after base-exchange reaction with certain organic ammonium salts showed a decided aversion to water and a remarkable tendency to swell in various organic liquids (53). In fact, the treated bentonite swelled to a much greater extent in some organic systems than the untreated counterpart in water.

Jordan and his co-workers (52, 53, 54) studied the gel-volume and gel-strength of many alkyl-substituted ammonium bentonites in different organic media and concluded that the degree of solvation depended upon at least three factors:

- a) The extent of the surface coating of the clay by organic matter. It was noted that solvation was negligible until a chain length of ten carbons was reached.

Approximately 50 per cent coverage was necessary for the development of a definitely organophilic character and the more completely the clay particle surfaces were covered with organic material, the more organophilic the clay became.

- b) The degree of saturation of cation exchange capacity. It was an important factor as shown by the fact that the maximum gel volume or viscosity was attained at nearly the region of complete cation exchange. This corresponded to the condition of maximum flocculation of the micelle.
- c) The nature of the solvating liquid. It was shown that the most effective solvation was obtained in liquids which combined highly polar with highly organophilic characteristics, such as nitrobenzene, or an alcohol-toluene binary system.

In explaining the role played by the polar member of such liquids it was postulated that, in the case of an incompletely clad complex, adsorption of a highly polar molecule on to the uncoated portions of the montmorillonite units, affected a further separation of the plates. It also completely covered the surface with organic material, thus making the surface more compatible with the surrounding liquid phase, and as a result, more readily available for solvation.

Arguments for the validity of the postulate were based on observations that at optimum concentration of polar liquid, gel volume varied directly with polarity

of the alcohol used. Also with increasing size of the alcohol molecule, increasing concentrations of that alcohol were needed to obtain maximum gelling. It was further illustrated that complexes characterized by complete coating of the clay flakes could be gelled in single non-polar systems.

Thixotropy was also demonstrated with organic bentonites in linseed oil and petroleum lubricating oil sols. This phenomenon was restricted to clay complexes prepared from quaternary ammonium compounds of large molecular size (53).

B. X-Ray Diffraction Data

It was found that each group of clay minerals had a characteristic layer thickness, which could be measured by x-ray technique (55). The basal spacing of montmorillonite was usually considered to be controlled by the nature of the exchangeable cations held between unit sheets, and the condition of hydration (15). When moisture-free, the basal spacing of montmorillonite was reported to be about 9.6 \AA . The interlayer expansions of montmorillonite in various liquids were shown to be determined by the size, charge, total amount of interlayer cations, the magnitude of the dipole moment, and the dielectric constant of the immersion liquid (56).

When the inorganic cations on montmorillonite were replaced by ammonium ions with large substituted groups the lattice spacing was expanded. Gieseke noted that the spacings were not always dependent on the dimension of the organic cations in

the free state, and did not vary with water content of the system (43). By tracing n-primary aliphatic ammonium bentonite complexes with an X-ray spectrometer, Jordan observed a stepwise separation of the flakes as the length of the amine chain attached to the clay was increased (52, 54). These steps were of the order of 4 \AA or approximately the van der Waals diameter of a methyl group. These data indicated that the hydrocarbon chains lay flat along the surface with the plates of the zig-zag chain parallel with the basal plane of the mineral. In the case where the organic chain occupied no more than half of the available area, the organic molecules on the top surface of one lamina might fit into the gaps between those on the bottom surface of the lamina directly above it, so that the resulting separation of the two laminae was only the thickness of one hydrocarbon chain. Where the chains were longer and occupied more than 50 per cent of the surface area, it was obvious that adjacent flakes would be unable to approach any more closely than the thickness of two hydrocarbon chains, or 8 \AA .

Jordan also found that the basal plane spacing of dimethyldidodecyl ammonium complex was 18.6 \AA and consequently a 9.0 \AA spacing for the organic molecules, which illustrated that the two long chains lay flat on the surface. If the chains were to extend out more or less perpendicularly to the surface, there would be a basal spacing of about 29 \AA required (52).

Rosauer et al. showed that treatment of bentonite with dialkyldimethylammonium salts in an amount less than the exchange capacity resulted in lattice expansions to 13 \AA and 10 \AA . While

clays treated with the ammonium salts equal to, or in excess of the exchange capacity, showed spacings of 32.8 Å; which coincided with basal spacings of the pure chemicals and indicated a multi-layer organic coating on the clay (57).

Byrne studied the x-ray diffraction of fifteen samples of pure montmorillonites from different deposits treated with ethylene glycol, piperidine and dodecylamine and showed that there was no relationship between the basal spacing of the untreated montmorillonites and their organic complexes. Apparently each clay adsorbed each organic compound to a different extent (58).

C. Differential Thermal Analysis Data (DTA)

The differential thermogram of bentonite was shown to be characteristic for identification purposes (59, 60). The curves showed an initial endothermic peak at 100° to 250°C, apparently representing the loss of water held between the basal planes of the lattice structure. There was a second endothermic peak between 600° to 700°C corresponding to the loss of lattice water. The third endothermic peak occurred at about 900°C indicating the final breakdown of the montmorillonite lattice, which appeared to be a unique characteristic of three-layer clay minerals. The third endothermic reaction was followed by a sharp exothermic effect probably accompanying a shift in bonding from face-sharing octahedral units to more stable edge-sharing units which normally existed in high temperature structure (61).

Differential thermal data are valuable for clay-mineral identification, and in some cases quantitative estimates have been made solely on such data. However, trustworthy identifi-

cation can be made only on the basis of several types of analytical data, e.g., differential thermal plus x-ray diffraction plus chemical data (62).

When montmorillonite was modified by organic cations, the predominant thermal reactions of the organo-clay were exothermic, indicating a combustion of the adsorbed cation. For large amine or quaternary ammonium complexes of montmorillonite the exothermic reaction started at around 200°C. It was noted that there was an endothermic shoulder at around 350° to 400°C, indicating dehydrogenation of entire aliphatic chains (58, 63). It was then followed by one or more peaks at higher temperature. The temperature at which these later peaks occurred seemed to be related to the composition of the clays. It was shown by Allaway (64) that the reaction took place in a stepwise manner, exhibiting "peaks" of exothermic activity, with a marked tendency for the reaction to subside during the intervals between the peaks.

Jordan (52) recorded the differential thermal curves for untreated montmorillonite and for butyl-, dodecyl- and octadecyl amine complexes of the same clay after exposure to an atmosphere of 75 per cent relative humidity for four days. These curves showed a progressive decrease in the size of the low-temperature endothermic peak of montmorillonite. This decrease resulted from the loss of adsorbed water with an increase in the size of the aliphatic chain.

Allaway (64) worked with piperidine-montmorillonite complexes and felt that the organic portion held by the clay broke down on firing with a loss of hydrogen, leaving a coating of carbon on

the external surface and between the unit layers of the clay mineral. The carbon was burnt off rather slowly as long as the clay mineral structure remained intact, but when the structure itself broke down, the carbon was quite rapidly oxidized.

D. Toxicology

An examination of Bentone 34^a, a commercially available dimethyldioctadecyl ammonium bentonite was made by the Food Research Laboratories, Inc.^b The following general conclusions were reported: (65, 66).

1. The oral LD₅₀ for rats was found to be 4.44 g. of dimethyldioctadecyl ammonium chloride/Kg body weight, or 6.35 g./Kg expressed as Arquad 2HT^c, (the organic portion of the complex).
2. The organic clay was inert when applied to the intact or abraded skin of rabbits or when instilled in the form of a suspension into their eyes.
3. It was non-allergenic when injected intracutaneously into guinea pigs.

a: Trade Name. A product of National Lead Company, Hightstown Laboratories, Box 420, Hightstown, New Jersey.

b: Food Research Laboratories, Inc., Long Island City, New York.

c: Trade Name. A commercially available brand of quaternary ammonium salts manufactured by the Armour Industrial Company, 100 University Ave., Toronto 1, Canada.

4. There was no significant impairment of growth, food utilization, hemoglobin level or red or white blood cell count, when fed at dietary levels as high as 25 per cent. At these concentrations, gross autopsies of the livers and kidneys gave no indication of a toxic reaction.

Similar studies on other organo-bentonites could not be located. However, their closely related composition, with respect to both mineral and organic components would seem to indicate that a comparably low order of toxicity could be expected (65).

E. Stability

a) Effects of pH

The alkylammonium bentonites are chemically neutral, their presence does not affect the pH of an organic liquid. They are resistant to the action of dilute acids and alkalies in a working range of pH 4 to 10, and maintain gel stability over extended storage periods in this range. However, prolonged contact at a lower or higher pH value may cause decomposition of the gellant, with consequent reduction of gel strength (65).

b) Effect of Heat

The alkylammonium bentonite contains trace amounts of water in its crystal lattice and this moisture is necessary for maximum gelling properties. Removal of this associated water detracts from its gelling efficiency. It should therefore never be stored at temperatures above 140° to 150°F (65).

Once the products have been properly gelled, it is stable in

service up to moderately high temperatures. Short exposures to temperatures as high as 325°F have no effect. On prolonged exposure in the 300-350°F range, however, some yellowing begins to occur, apparently due to the splitting off of minute quantities of the organic component. Where color is not a factor of importance, they have performed in industrial compositions at temperatures as high as 400°F for sustained periods of time with little or no loss of efficiency (65).

Billups (67) determined the breaking temperature of ointment bases thickened with Bentone gellants and indicated the grease-type bases were stable to 180°C with a slightly yellow coloring. He suggested it could be used in ophthalmic preparations where sterilization with heat was necessary.

c) Resistance to Solvent Washing

It had been demonstrated (68) that for dimethyldioctadecyl ammonium bentonite, a small portion of organic material could be removed by extraction techniques. A low polar solvent could remove up to 4 meq. of the organic cation per 100 g. of complex, while a high polar liquid would remove 10 to 12 additional meq. of the organic material. However, Cown and White showed that when excess amounts of large ammonium ions were adsorbed on the clay lamina, they were not removed by water-washing due to the strong van der Waals forces of the large molecules (46).

d) Exchange Reaction

It had been observed that under some conditions of use, some types of organo-clay complexes appeared to undergo decomposition.

One mechanism that had been proposed (69) was that the organic cations that were originally held on the clay became exchanged for some other cation present in the dispersion medium. If such exchange took place the nature of the organo-clay might be altered sufficiently to cause a change in its rheological properties, since it was well recognized that such properties were highly dependent on the organic material associated with the clay.

In a series of studies (69, 70) McAtee found that this organic-organic ion exchange on montmorillonite did take place, although the degree of exchange was relatively low. It was also demonstrated that when a very large excess of sodium ion was present in the medium it could also exchange with the large ammonium ion on the montmorillonite surface with the consequence of decreasing the gelling ability of the complex.

APPLICATIONS OF ALKYLAMMONIUM BENTONITES (71,72,73)

Certain commercially available organic bentonites are widely used today in the lubricating industry to thicken oil to a grease. The non-melting and temperature-independent characteristics, the unusual mechanical stability and complete water resistance of the resulting grease make it superior to conventional greases for many purposes.

The manufacturers of paints, lacquers and stains have taken advantage of the unique properties of these organic bentonite complexes to improve their products. Reduction of gloss and spectral reflection of the lacquers, improvement of

settling characteristic and brushability of pigments and paints, prevention of sagging and run-off of coatings, and the achieving of a tough, uniform and more resistant film after the paints have dried are a few of the utilizations claimed for these products.

Successful applications such as compounding and reinforcing ingredients for elastomers and plastics, increasing hardness and heat resistance for asphalts and waxes, water-in-oil type drilling fluids, adsorbents for gas chromatography, textile greases, dye receptors in fiber, soil conditioners, viscosity control in resins, insulative materials and sealants in buildings are all well known.

In the pharmaceutical field, the complex was found to be satisfactory for gelling hexamethyltetracosane, which is a saturated, liquid hydrocarbon of animal origin. The gel was reported to be hypo-allergenic, skin permeable, inert and compatible with many medicaments (74). Mineral oil thickened with a commercial gellant (Bentone 38*) was evaluated as an ointment base along with other commonly used bases by Billups and Sagar (75, 76). A number of advantages were claimed for these materials. Among these were: (a) extremely stable to high and low temperature (b) little change in consistency with change in temperature, (c) compatible with most widely used dermatological medicaments, (d) great spreadability when applied to skin, (e) large capacity for solid ingredients, (f) great water adsorbing properties,

*Trade Name

(g) rapid drug release, and (h) easy handling and manufacturing.

The organo-clay was also considered as a tablet granulating and binding agent for hydrolabile drugs. A moisture-free, organic solvent could be selected as the dispersing medium. The granules thus formed were loose, fluffy and suitable for tabletting. A shelf test was also carried out for the tablets prepared from different granulating agents. For certain drugs, a more stable tablet preparation was obtained when the organo-clay was used as the binder than when another commonly used aqueous binder such as liquid glucose was employed (77).

STATEMENT OF PROBLEM

Since the development of quaternary ammonium bentonite complexes, the inherent properties of these compounds have roused an ever increasing interest. As one result of this, industrial applications have continued to increase until today a sizeable market exists for such products. As knowledge of their properties became better known, it became apparent that such materials could be of value as medicament carriers, particularly in topical applications.

The pharmaceutical acceptability of known bentonite deposits in the Province of Alberta had been evaluated by Anderson and Plein (78,80). They demonstrated that wide differences in physical properties existed among the clays taken from different deposits. It was considered a reasonable assumption that these differences would carry through to the organic complexes prepared from such clays. If this should prove to be true, then organo-

bentonites should exhibit measurable differences depending upon the deposit from which the original clay was taken. In addition, any success achieved in a study of such complexes prepared from Alberta clays could have an impact on the economic potential of these reserves.

Only a few studies had been conducted previously on the utility of organo-clay complexes in pharmaceutical preparations. It was felt, therefore, that a comparison of the relative usefulness of complexes prepared from bentonites taken from known deposits in the province would contribute valuable information on the subject.

In order to obtain such information, samples of bentonite would be collected, representative of different deposits located throughout the province. After purification, each sample of clay would be reacted with quaternary ammonium compounds of large molecular size. The products obtained would be subjected to physical tests to obtain some degree of characterization. Finally, the utility of the organo-bentonites as gellant and emulsifying agents for ointment and lotion bases would be evaluated through experimentation with selected dermatological medicaments.

EXPERIMENTAL

In designing this project, it was decided to divide the work into three main phases: (1) selection of the native Alberta bentonites, (2) preparation and testing of bentonite-organic complexes and (3) formulation and pharmaceutical evaluation of lotions and ointment bases as medicament carriers.

PART I SELECTION AND TESTING OF NATIVE ALBERTA BENTONITES

All clays employed in this study were obtained from a collection of bentonites maintained in the Faculty of Pharmacy. The samples comprising this collection represented all known deposits within the Province of Alberta and had been collected over a period of several years through field trips and individual donations (78) .

Because of a continuing program of studies based on these clays, certain lots were used up more rapidly than others. When this situation developed, it was necessary to re-visit such beds in order to replenish the supply. Material obtained on such trips was accorded a separate number for identification purposes. Such a procedure was considered to be desirable because of the known lack of uniformity in physical characteristics among samples even when taken from the same deposit. To reduce such differences to a minimum, every effort was made to obtain subsequent samples from the original exposure sites.

Identification of each clay in the collection had been

completed prior to the selection of samples for this work. Methods employed involved field tests by qualified geologists and, where possible, instrumental analyses based on x-ray and thermal techniques (78, 79) .

A. Index of Bentonites Employed

Sample 29-- A fifty pound bag of B, C. Volclay^a. This material had been found earlier to be a high grade bentonite which met all minimum standards of the U.S.P. XV^b and B.P. 1958^c. Since such standards remained unchanged in the U.S.P. XVII and B.P. 1963, it was employed here as a control clay.

Sample 34-- Obtained through the Magcobar Mining Company^d from their lease at Rosalind. This grade of material was reported in recent publications as Sample 1-A (78, 80) .

a-- Trade name of a grade of bentonite received from the American Colloid Company, Merchandise Mart Plaza, Chicago 54, Illinois, U.S.A.

b-- The Pharmacopoeia of the United States of America, Fifteenth Revision.

c-- The British Pharmacopoeia, 1958

d-- Magcobar Mining Company, Ltd., Calgary, Alberta.

Sample 35-- Obtained from the Magcobar Mining Company.

Claimed to be high in "ash" content, this particular commercial product was taken from Section 5 of the Rosalind lease.

Sample 37-- This material was collected from a cutbank of Black Mud Creek approximately two miles from the junction with White Mud Creek in south Edmonton. The bed showed evidence of trenching and extensive sampling.

Sample 38-- This clay was found in the Bickerdike area west of Edmonton. Location was determined to be in Secs. 6 and 7, Tsp. 52, R. 18, W. 5. A later report gave the location at "Mile 6, Coalspur branch of the Canadian National Railway" (81).

Sample 39-- A product of the Magcobar Mining Company lease at Rosalind, this sample was recovered from a core drilling test program designed to determine the extent of the beds in the lease. It was labelled by the company as DH 58 when received for the collection.

Sample 40-- Obtained from the upper portion of a slump on the Smoky River. A sample from the same spot was examined earlier as Sample 27 (78, 80).

Sample 41-- Same location on the Smoky River as for Sample 40. However, this material was taken from the bottom of the showing in question and

differed somewhat in physical appearance.

Sample 44-- Collected from a showing in the Kleskun Hills, this clay was taken from the same hole as Sample 25 (78).

Sample 45-- A most interesting bentonite sample was obtained from a showing on the bank of the Rosebud River in the Beynon vicinity in 1958. This was at that time designated as Sample 5 (78). Subsequent laboratory requirements depleted the stock to a point where the supply had to be replenished. The new supply was taken as close as possible to the original workings and labeled Sample 45.

B. Preparation of Samples

Clays obtained from the departmental collection in each case were in the form of a "mill run" powder. According to Anderson (82), the original preparation procedure was as follows: "Field samples were broken into small pieces about one-half inch in size. Coarse contaminants were removed by hand and the clay was dried over night in an oven set at 70°C. The dried material was then passed through a swing hammer mill and sifted to pass a screen containing 200 meshes to the inch". In cases where samples were received as a fine powder, the material was simply sifted as above through a 200 mesh screen.

In this investigation the samples to be studied were reduced to a fine powder where necessary, using the above procedure.

Purification

Mechanical analysis data indicated that native Alberta bentonites contained a significant amount of silt and sand. Anderson reported values for such fractions ranging from 6 to 60 per cent (80).

Sand, silt and clay are fractions of soil which differ in size. Thus, according to the International (or Atterburg) procedure size limitations for each of these fractions are as follows (83):

	Maximum <u>Diameter</u>	Settling Velocity in Water <u>(at 20 °C)</u>
Coarse Sand	2.0 mm.	
Fine Sand	0.2 mm.	
Silt	0.02 mm.	10 cm. per 4.8 min.
Clay	0.002 mm.	10 cm. per 8.0 hours

From these data it was obvious that settling in water for twenty four hours would be sufficient to separate the clay fraction of the bentonite samples from the sand and silt portions. However, aqueous suspensions of the native bentonite were allowed to stand undisturbed for four days before separation of the supernatant clay portion in order to reduce the possibility of silt contamination to a minimum. Further to this, it was expected that the overall decrease in size of the clay particles recovered would be an advantage in the later synthesis procedures.

Procedure

A four per cent suspension of native clay in distilled water was prepared. This concentration was found to be sufficiently dilute to prevent the formation of thixotropic structure in the clay, which would have interfered with settling rates of the sand and silt. A Waring Blendor^{*} was employed for the initial wetting of the clay because of the high shear needed to prevent clumping.

The suspension was covered to prevent evaporation and accidental contamination, and left undisturbed for four days. The supernatant liquid containing the clay fraction was then removed by siphoning from the compact deposit of sand and silt found on the bottom of the container. This aqueous dispersion was transferred to evaporating pans, which were placed in a forced air oven set at 100°C to remove the bulk of the water. The drying process was then completed at a temperature of 70°C. Finally, the residue was ground to a 200 mesh powder and stored in containers with close-fitting lids.

C. Limit Tests

A rigorous chemical analysis of the selected clays was not attempted in this study. It was felt that such data would be of little value in view of the nature of the investigation. On the other hand, certain physical properties were considered to

*Trade Mark

have a direct bearing on the selection of clays for use in complex formation.

While some of the deposits from which these clays were taken had been subjected to such tests prior to this study, the known variability within bentonite beds made it desirable to repeat the procedures. Accordingly, a number of limit tests as found in the B.P. were undertaken in order to obtain data which would assist in determining which samples would be suitable for further study.

a) Alkalinity

The B.P. (84) states that a 2.0 per cent w/v suspension of bentonite in distilled water should record a pH of 9 to 10.5.

Procedure: Two grams of clay was added in small portions to 75 ml. of deionized distilled water in 100 ml. Pyrex graduated cylinder. After all of the clay had been added and had settled to the bottom of the cylinder, more deionized water was added to volume. The contents were then transferred to a 250 ml. Pyrex beaker containing a Teflon-coated stirring bar and the assembly was placed on a magnetic stirrer. The contents were stirred at a rapid, uniform speed and readings were taken with a Beckman Zeromatic pH meter using a Calomel-glass electrode combination. Each sample was prepared at least in triplicate and data obtained are presented in Table I.

With the exception of Sample 39, all clays gave a pH within official limits. In general, no significant change in pH occurred as a result of purification, although Sample 34 showed considerable reduction in alkalinity (0.4 pH unit).

TABLE I

pH VALUES OF ALBERTA BENTONITE AQUEOUS SUSPENSIONS
(2.0 PER CENT W/V)

Sample	pH Values			Average
29-C ^{a, b}	9.5	9.5	9.5	9.5
29-P ^c	9.6	9.6	9.6	9.6
34-C	9.4	9.4	9.4	9.3 ^d
	9.2	9.2	9.2	
34-P	8.8	8.9	8.8	8.9 ^d
	9.0	9.0	9.0	
35-C	9.5	9.5	9.5	9.5
35-P	9.4	9.4	9.4	9.4
37-C	9.9	10.0	10.0	10.0
37-P	9.9	9.9	9.8	9.9
38-C	9.8	9.8	9.8	9.8
38-P	9.8	9.8	9.7	9.8
39-C	8.6	8.7	8.7	8.7
39-P	8.3	8.3	8.3	8.3
40-C	9.9	9.9	9.9	9.9
40-P	9.6	9.6	9.7	9.6
41-C	9.8	9.8	9.8	9.8
41-P	10.0	10.0	10.0	10.0
44-C	9.9	9.8	9.9	9.9
44-P	9.8	9.8	9.8	9.8
45-C	9.8	9.8	9.8	9.8
45-P	9.9	9.9	10.0	9.9

a: C refers to crude sample

b: data obtained from reference (85)

c: P refers to purified sample

d: average of six determinations

An allowance for variability within individual bentonite deposits was made and on this basis, only the Sample 39 results were considered to be indicative of a substandard bed.

b) Swelling Power

The B.P. (84) requires that 2.0 g of bentonite must swell to an apparent volume of not less than 24 ml.

Procedure: Two grams of bentonite was added in 20 approximately equal portions at intervals of two minutes to 100 ml. of a one per cent (w/v) solution of sodium lauryl sulfate contained in a 100 ml. measuring cylinder. Precautions were taken in each case to prevent loss of liquid through evaporation. The mixture was allowed to stand undisturbed at room temperature for 12 hours, after which the apparent volume of clay was read.

The results of these determinations are presented in Table II and compared graphically in Figure 2.

From the values obtained, it was apparent that some of the crude bentonites were of the medium or low-swelling type. After removal of the non-clay portion, however, they all showed high swelling power. In particular, the purified clay from the Beynon deposit (Sample 45) was found to be outstanding in this respect.

TABLE II
Alberta Bentonites
Swelling Test, B.P. 1963

Sample a, b	Apparent Volume in ml. of hydrated clay			Average
29-C ^c	40	40	40	40
29-P	44	43	43	43
34-C	29	29	29	29
34-P	49	48	47	48
35-C	28	28	29	28
35-P	35	34	33	34
37-C	22	23	21	22
37-P	55	50	50	52
38-C	9	8	9	9
38-P	24	24	24	24
39-C	32	33	33	33
39-P	42	43	42	42
40-C	25	24	25	25
40-P	28	28	28	28
41-C	15	11	13	13
41-P	33	35	34	34
44-C	21	23	23	22
44-P	47	46	47	47
45-C	19	18	18	18
45-P	72	72	72	72

a: Determinations on each sample were done in triplicate.

b: -C Crude sample
-P Purified sample

c: Data obtained from reference (86)

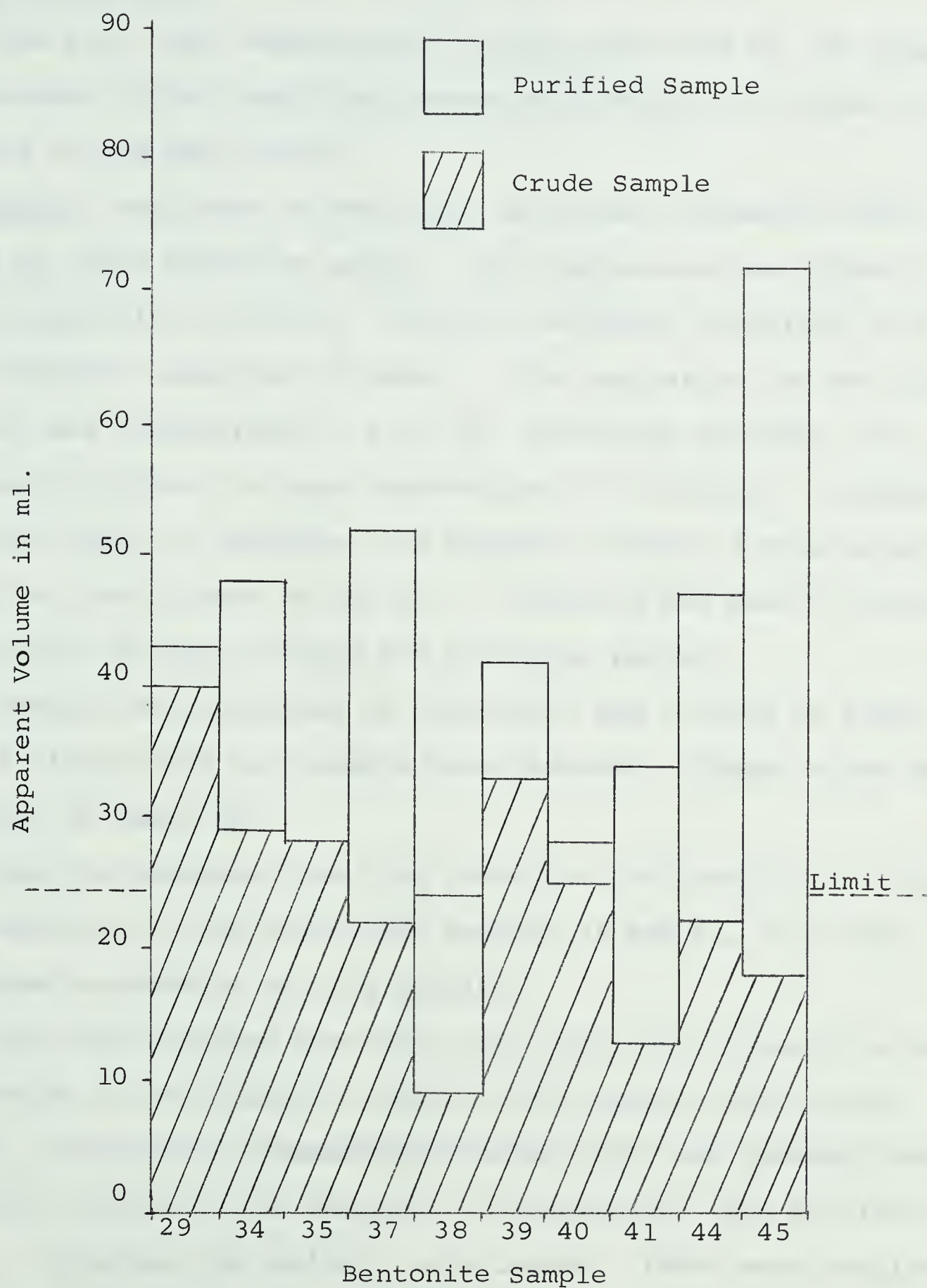


Fig. 2. Swelling Power of Alberta Bentonites

B. P. 1963 Method

c) Gel Formation

The B.P. (84) requires that no more than two ml. of clear supernatant liquid should be separated from the gel proper by the end of the test period.

Procedure: Six grams of bentonite was mixed intimately with 0.3 grams of light magnesium oxide. The mixture was then added in small quantities to 200 ml. of distilled water contained in a 500 ml. stoppered measuring cylinder. After agitation for one hour, 100 ml. was transferred to a 100 ml. measuring cylinder, and allowed to hydrate at room temperature for 24 hours. A reading was then taken to determine the apparent volume of supernatant liquid on the surface of the gel. Provision was made to prevent evaporation of water during the hydration period.

Samples were prepared in triplicate and volumes of supernatant liquids for each sample were observed. These values are reported in Table III.

Results obtained from this procedure indicated that, with the exception of the unpurified Samples 38 and 41, all clays possessed acceptable gelling quality.

The data obtained from the limit tests were taken into consideration in selecting the clays to be employed for further study. In addition, commercial availability, and geographical location influenced the decision. Accordingly, five purified clays, including the control, were chosen. These were Samples 29, 34, 38, 44 and 45.

TABLE III
Alberta Bentonites
Gel Forming Test--B.P. 1963

Sample ^a	Apparent Volume, in ml. of Supernatant Liquid			Average
29-C ^b	1.5	1.5	1.5	1.5
29-P	0	0	0	0
34-C	0	0	0	0
34-P	0	0	0	0
35-C	0	0	0	0
35-P	0	0	0	0
37-P	0.5	0.5	0.5	0.5
38-C	73	73	75	74
38-P	0.5	0.5	0.5	0.5
39-C	1	1	1	1
39-P	0	0	0	0
40-C	1	1	1	1
40-P	1	1	1	1
41-C	23	18	23	21
41-P	0	0	0	0
44-C	-	1	2	1.5
44-P	0	0	0	0
45-C	0	0	0	0
45-P	0	0	0	0

a: -C Crude Sample

-P Purified Sample

b: Data taken from reference (87)

D. Rheology of Bentonite Magmas

a) Apparatus

A concentric cylinder rotational viscometer was required to determine the rheological properties of the prepared fluid dispersion. For this purpose, a Fann V-G Meter Model 35* (Serial No. 1907) was employed.

With this instrument, fluid was contained in the annular space between the two co-axial cylinders. This space was filled to a predetermined height with the liquid to be tested. The outer cylinder, or rotor, was suspended in a precision bearing and was driven at a constant angular velocity. The torque arising from the viscous drag of the fluid was exerted on the inner cylinder, or bob. This stress was rapidly balanced by a helically wound spring, and the deflection was read on a calibrated dial through an optical reticule. In this manner, the flow was read in terms of shear rate (proportional to rotor speed) and shearing stress (proportional to the dial reading).

As received from the manufacturer, the Fann viscometer is a simple-to-operate instrument with rotor speed changes for 3, 6, 100, 200, 300 and 600 r.p.m. These changes can be made without stopping rotation. To accomplish this, a three-position gear shift is employed in conjunction with a two-position switch controlling the motor speed. The rotor is driven by a 115 volt,

*Manufactured by the Fann Instrument Corporation, Houston, Texas, U.S.A.

60 cycle dual-speed synchronous motor.

In order that better control could be maintained over rheological properties of the fluids under test, additional rotor speeds were obtained by interposing a 9:1 reduction gear between the motor and the rotor. This made available a total of twelve rotor speeds, but experience later indicated that rotor speeds in excess of 300 r.p.m. were not required.

Accuracy of the indicated rotor speeds was determined with the aid of a stop watch for the lower speeds and with a Strobotac* for the higher speeds. Agreement ranged from exact for the low speeds to an error of less than one per cent at 300 r.p.m.

During the actual determinations, temperature of each dispersion was controlled by placing the sample in a double-walled copper cup. Water at a temperature of 30°C from a Sargent constant temperature bath** was pumped through the cup jacket and returned to the water bath.

Calibration of Torsion Spring in Fann Viscometer

For this work, a Fann Spring No. 27 S was installed in the instrument. This spring was found to be sufficiently sensitive to yield satisfactory dial deflection readings. Calibration was done by the "dead weight" method as recommended by the supplier.

* Trade Name--Type 1531-A, General Radio Company, Concord, Mass. U.S.A.

**Sargent Thermonitor Controlled Water Bath. Serial No. S-84810, E.H. Sargent and Company, Chicago, Illinois, U.S.A.

$$K_s = \frac{G g R}{\theta}$$

Where K_s = Spring constant in dynes cm./degree

G = Load in g.

g = Gravitational acceleration, 981 cm./sec²

R = Radius arm in cm.

θ = Dial reading

Radius of bob (R) = 1.73 cm.

Load in g. (G) = 10.00 g.

Dial Reading (θ) = 272.0

Then

$$K_s = \frac{10 \times 981 \times 1.73}{272.0} = 62.4 \text{ dynes-cm./degree}$$

The spring constant (K_s) represents the torque per degree of arc through which the dial has been rotated. Thus dial reflection may be converted to torque in dyne cm. by multiplying the dial reading by K_s .

b) Bentonite Magmas

Rheological studies of Alberta bentonites yielded data which, when plotted in the form of a standard rheogram, fitted the model of "plastic flow" (88). However, it was evident from such data that consistency of these systems varied widely among the different clays studied.

For this reason, it was felt that data of this nature should be obtained in order that a comparison of rheological properties on selected bentonites could be made. Subsequent rheograms of corresponding organo-bentonite dispersions could also be compared with these to determine whether any correlation of viscosity would be obtained.

Procedure

Fifteen grams of powdered bentonite was added to 285 grams of distilled water under agitation in a Waring Blendor. Mixing was continued at low speed for five minutes. The five per cent (w/w) magma was then allowed to hydrate undisturbed for 24 hours in a closed jar.

Prior to use of the viscometer, the hydrated sample was allowed to come to equilibrium temperature (30°C) by placing the closed jar in a water bath. The contents of the jar were then mixed thoroughly and transferred to the double-walled viscometer cup. The cup was properly fitted to the instrument and readings were taken at 15 second intervals. Values obtained are reported in Table IV and presented graphically in Figure 3.

TABLE IV

DIAL DEFLECTION READINGS OBTAINED FOR 5 PER CENT (W/W) BENTONITE MAGMAS

USING MODIFIED FANN VISCOMETER, TEMPERATURE 30 °C

FANN SPRING NO. 27S, $K_s = 62.4$ dynes-cm./degree

Bentonite Sample	Dial Deflections a, b, c, d									
	r.p.m.	3	6	11	22	33	67	100	200	300
	r.p.m.	r.p.m.	r.p.m.	r.p.m.	r.p.m.	r.p.m.	r.p.m.	r.p.m.	r.p.m.	r.p.m.
29 (Control)	22	28	32	41	47	62	74	106	134	
	10	12	18	22	29	44	60	99		
34	58	72	94	126	149	204	257			
	58	70	95	122	149	202				
38	2	3	4	6	7	12	17	32	44	
	2	4	6	7	10	14	19	33		
45	12	20	28	46	62	96	126	200	264	
	16	20	33	47	61	94	126	200		

a For each sample, the upcurve deflections are listed in the top line reading from left to right in ascending order. The down curve deflections are listed in the bottom line reading from right to left in descending order.

b Time interval between readings was 15 seconds.

c Each value represents an average of the readings obtained from two different magmas.

d For further details, see Appendix, Table I.

FIGURE 3

CONSISTENCY CURVES OF ALBERTA BENTONITES

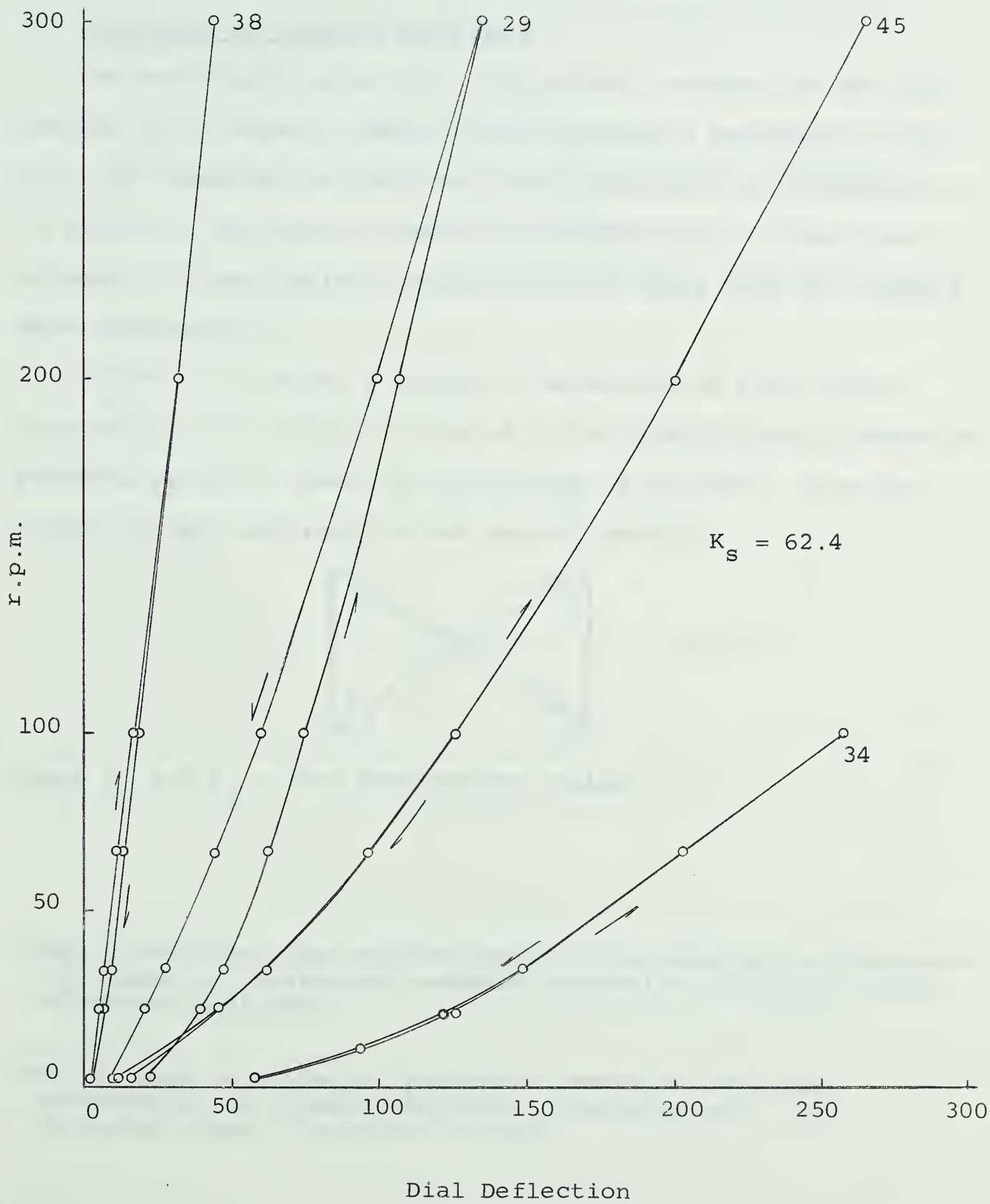
5% W/W

No. 29 (Control)

34

38

45

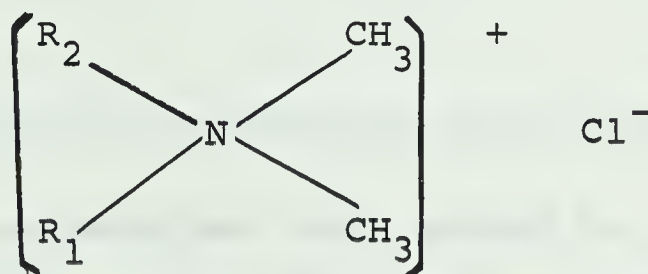


PART II PREPARATION AND TESTING OF BENTONES*

A. Selection of Organic Reactants

As previously noted (52), 50 percent coverage of the clay laminae by an organic compound was considered necessary to convert the character of the clay from hydrophilic to organophilic. In addition, quaternary ammonium compounds with at least two aliphatic groups having a chain length of more than ten carbons were recommended

Efforts to locate a supply of materials of this nature resulted in the receipt of stocks of two dialkyldimethylammonium products marketed under the trade name of Arquad**. The compounds chosen conformed to the general formula.



where R_1 and R_2 = long hydrocarbon chains

* For convenience the term "bentone" will be employed in this work to refer to quaternary ammonium bentonite complexes unless otherwise indicated.

**Trade name of a line of quaternary ammonium compounds produced by the Armour Industrial Chemicals Ltd., 100 University Ave., Toronto 1, Canada

According to information received from the manufacturer, the Arquads were not pure compounds but rather mixtures as indicated in Table V.

TABLE V
COMPOSITION OF ARQUADS EMPLOYED IN COMPLEX FORMATION

In Per Cent		
Alkyl Group	Arquad 2HT-75	Arquad 2S-75
Octyl	-	-
Decyl	-	-
Dodecyl	-	-
Tetradecyl	-	-
Hexadecyl	24	24
Octadecyl	75	4
Octadecenyl	1	30
Octadecadienyl	-	42

The products, as received, were stated to contain 75 per cent of active ingredient in a vehicle containing 0.5 per cent sodium chloride, 17 to 18 per cent of isopropanol, and 6.5 to 7.5 per cent of water.

Testing of each Arquad confirmed the supplier's statement that they were essentially insoluble in water. However, if prepared in hot distilled water, a uniform dispersion could be obtained.

Cation Exchange Capacity

As indicated earlier (52), the basis for synthesis of organo-bentonite complexes was a knowledge of the C.E.C. of each clay. Such data had been obtained previously for each of the five clays selected. This information is presented in Table VI.

TABLE VI

CATION EXCHANGE CAPACITY OF SELECTED BENTONITES ^a

Sample ^b	C.E.C. in meq. per 100 grams oven dry clay ^c
29	82.5
34	64.3
38	95.8
44	58.9
45	55.6

a Ammonium Acetate Method (89) .

b In all cases, values were based on samples not subjected to purification by water sedimentation.

c Unpublished data obtained from laboratory records of Dr. A.J. Anderson.

B. Preparation of Bentones for Preliminary Studies

Several methods had been reported for the preparation of organo-bentonite complexes. Of these, a procedure involving an exchange reaction in an aqueous medium was considered to be the most effective. Since adsorption of the quaternary ammonium ion by montmorillonite was shown to occur instantaneously, the reaction was effected by simple mixing (52).

From the C.E.C. values as presented in Table V, it was apparent that 100 meq. of Arquad per 100 grams of oven dry clay should be sufficient to cover all of the exchange positions on the clay surface and so ensure a complete reaction. As a result, this value was chosen for use throughout this series in order to obtain bentones suitable for subsequent screening tests.

On this basis, 78 grams of Arquad 2HT-75 and 72 grams of Arquad 2S-75 were employed to react with 100 grams of bentonite sample.

Procedure

A four per cent dispersion of bentonite was prepared by the addition of 100 grams of clay to the required amount of distilled water. The bentonite was allowed to hydrate overnight and was then heated with stirring to 70°C. The required amount of quaternary ammonium salt previously prepared at a concentration of one or two per cent by dispersing in hot distilled water, was added slowly with vigorous stirring. Reaction was accompanied by thorough flocculation in most cases. Agitation was continued for 30 minutes as a precautionary measure to ensure a complete reaction. The flocculent precipitate was then

filtered under reduced pressure through a large Buchner funnel, and was washed with several portions of hot distilled water until the washing gave a negative test for chloride ion. The filtered cake was then dried in an oven at 65°C, pulverized in a laboratory hammer mill and passed through a #100 mesh screen.

In this manner each of the five purified clays was reacted with Arquads 2HT-75 and 2S-75 to form the corresponding bentones. Products were labelled to include the sample number of the purified clay component as well as the Arquad number, i.e., 29-2HT-75 and 29-2S-75.

C. Selection of Medium for Gelling Systems

Jordan et al, found that the most effective solvating liquids for organic bentonite complexes were those combining highly polar and highly organophilic properties (52, 53, 54). Later Billups (90) confirmed this finding. In preparing ointment bases from Bentone 38*, excellent gelling characteristics were obtained by using an alcohol-mineral oil combination as the dispersing medium. From data presented in the study, 50 per cent of 95% alcohol (based on the weight of bentone used) appeared to be the optimal concentration for the system. Such result was in agreement with the recommendations of the National Lead Company (91). Consequently, this solvent combination was employed throughout the rheological and formulation studies, with the minor modifications as indicated.

Alcohol U.S.P. contains not less than 92.3 per cent by weight

*See footnote p. 50

(or 94.9 per cent by volume), at 15.56°C, of C_2H_5OH . This alcohol was obtained as a 95 per cent (v/v) product and was employed throughout this study.

Mineral Oil: A supply of liquid petrolatum, claimed to be of U.S.P. grade, was obtained from the Imperial Oil Company** for use in this study. Marketed as Marcol 70, the oil was stored in five gallon containers. Data supplied by the Company indicated the oil had a specific gravity of 0.863 and a viscosity (SUS at 100°F) of 70 seconds.

This "light" viscosity oil was chosen since it was intended for use in preparing both ointment bases and lotions. In the latter case, a reduction in greasy "feel" was considered desirable.

D. Screening of the Prepared Bentones

To determine relative gelling efficiencies of the bentones previously synthesized, it was decided to prepare dispersions of each in Marcol 70, and determine the consistency of the sols. Alcohol was used to "trigger" the gelling. Readings were then taken with the Fann viscometer.

As recommended by Billups (92) and the National Lead Company (93), Bentone 38 was chosen as the control since it was considered to be the gellant of choice in a predominantly mineral oil system.

*Trade name of a commercially available organic derivative of a special magnesium montmorillonite, produced by the National Lead Co., 105 York Street, Brooklyn, N.Y.

**Imperial Oil Company, Edmonton, Alberta

Procedure

Nine grams of bentone was added to 286.5 g. of Marcol 70 under high shear in a two-speed Waring Blendor. To maintain a uniform control of r.p.m., the Blendor was coupled with a variable rheostat. Preliminary tests established the proper setting for the rheostat, and this setting was not changed throughout this experiment.

Agitation was continued for 15 minutes, a 4.5 g. quantity of alcohol was then added to the dispersion and mixing was continued for another 15 minutes. The three per cent (w/w) dispersion was then transferred to a glass jar, covered, and placed in a water bath at 30°C for 30 minutes. No aging period was required to develop maximum gelation, since full viscosity development was obtained immediately after proper dispersion of the Bentone gellant (94). Contents of the jar were then transferred to the double-walled viscometer cup. Readings were taken at 3, 6, 11, 22, 33, 67, 100, 200 and 300 r.p.m. at intervals of 15 seconds.

The sole purpose of this procedure was to obtain information regarding the relative gel-forming abilities of the ten bentones as a basis for selecting a more convenient number of products for further testing. For this purpose, it was felt that a preliminary "scan" of a qualitative nature only would be sufficient to permit making such a choice. Values for both up-curve and down-curve were recorded for each bentone including the control, and are presented in Table VII.

On the basis of the consistency values obtained and the pharmaceutical acceptability of the products, the following bentones were selected for later use in preparing the proposed medicament carriers: Bentone 38 (control), bentone 29-2HT-75, bentone 34-2HT-75, bentone 38-2HT-75 and bentone 45-2S-75.

The 2S-75 complexes were less suitable due to the development of an unpleasant odor of the sols on prolonged standing. However, bentone 45-2S-75 was included in spite of the slight odor since its gelling characteristic was decidedly superior to that exhibited by the 45-2HT-75 complex. It was not considered objectionable in an organoleptic sense.

TABLE VII

CONSISTENCY DATA FOR SCREENING BENTONES ^{a,b}

(3% w/w in Marcol 70 with 1.5% Alcohol)

- a. For each sample, the up-curve deflections are listed in the top line reading from left to right in ascending order. The down-curve deflections are listed in the bottom line reading from right to left in descending order.
- b. All readings taken at 30 °C.

TABLE VII
CONSISTENCY DATA FOR SCREENING BENTONES

Sample	Dial Deflection									
	3 r.p.m.	6 r.p.m.	11 r.p.m.	22 r.p.m.	33 r.p.m.	67 r.p.m.	100 r.p.m.	200 r.p.m.	300 r.p.m.	
Marcol 70	4	5	6	10	14	25	38	72	106	
	4	5	8	10	14	25	37	71		
Bentone 38 (Control)	58	64	74	96	114	155	194	289		
	63	70	83	100	119	158	198			
29-2HT-75	12	15	19	28	34	56	78	134	184	
	12	14	19	26	32	52	74	130		
29-2S-75	6	10	14	24	32	53	76	134	182	
	6	9	14	21	27	46	68	126		
34-2HT-75	8	12	17	26	35	57	81	139	190	
	10	11	17	24	32	52	74	132		
34-2S-75	11	15	22	34	44	72	100	170	226	
	12	15	20	30	38	63	89	157		
38-2HT-75	22	24	28	37	47	71	95	158	212	
	18	19	25	32	39	61	83	140		
38-2S-75	8	12	17	25	34	54	76	131	176	
	9	10	16	22	29	48	70	123		
44-2HT-75	12	15	20	28	36	56	78	135	188	
	11	13	18	26	32	52	74	131		
44-2S-75	10	13	17	24	33	54	76	134	187	
	10	12	16	23	30	51	74	131		
45-2HT-75	11	14	20	29	38	62	88	152	212	
	11	14	18	28	35	58	82	144		
45-2S-75	91	94	100	112	125	163	206	295		
	82	84	94	101	120	156	194			

E. Preparation of Selected Bentones

a) Optimum Ratio of Bentonite and Arquad

On a commercial basis, Bentone products are reported to be manufactured on a basis of 100 meq. of quaternary ammonium salt to 100 grams of clay (95). This quantity of organic salt was apparently chosen on the basis of the generally accepted average C.E.C. values for Wyoming bentonites (100 meq.). However, since it was known that the clay selected for this study had C.E.C. values considerably less than 100 meq., it was felt that a brief study of this aspect might prove of some value.

As stated by the manufacturer*, "The Arquads are industrial chemicals. They are not intended to be of pharmaceutical specifications, such as many of the expensive refined grades of quaternaries now offered commercially". Also, there would appear to be room for doubt regarding the absolute accuracy of the C.E.C. values obtained for the clays chosen, since these values were obtained on the crude materials only. Finally, no completely satisfactory method has been developed for determining C.E.C. values, as evidenced by the number of methods advanced in the literature for determining such data.

In effect, then, it was felt that truly accurate ratios for the Arquads to react with clay could not be expected in any procedure designed to yield such information. Rather, it was recognized that data obtained would be indicative of a range sufficiently narrow to possibly result in bentones of a better

*Armour Industrial Chemical Company, "Arquads", p.3.

gelling property than those synthesized on the basis of an arbitrary 100 meq. per 100 grams of bentonite.

Accordingly, a series of bentones was prepared as before, in which the quantity of Arquad added was varied over a range. For convenience, such quantities of Arquads were expressed in meq. The bentones obtained were reduced to a fine powder and then dispersed in Marcol 70 as before. Consistency data of the up-curve for each oil dispersion were recorded and are presented in Table VIII. Dial deflections of the viscometer at 200 r.p.m. were plotted against meq. of Arquad added, as shown in Fig. 4. A maximum peak was obtained for each clay.

Major difficulties were encountered in attempting to obtain replicates of the data presented in Table VIII. It appeared that minor variations in the degree of surface coverage of clay particles had an important influence on the gelling properties of the resulting bentone. With this in mind, the optimum ratios for Arquads as presented in Fig. 4 were accepted as a guide. In the production of "pilot plant quantity", a slightly smaller amount of Arquad was added to the clay. Prior to filtration of the reactant mixtures, consistency curves were run on test aliquots of the mixture. These aliquots were dried, reduced to a fine powder, and dispersed in Marcol 70 as before. Where indicated, additional Arquad reactant was added to the mixture to obtain maximum gelling power.

TABLE VIII

CONSISTENCY VALUES OF BENTONE DISPERSIONS PREPARED WITH
VARYING QUANTITIES OF ARQUAD

a. Three per cent dispersion of Bentone 29-2HT-75

meq. of Argquad added/100 g. of clay	Dial Deflection a, b								
	3 r.p.m.	6 r.p.m.	11 r.p.m.	22 r.p.m.	33 r.p.m.	67 r.p.m.	100 r.p.m.	200 r.p.m.	300 r.p.m.
64	4	5	8	14	20	36	51	96	140
75	70	74	83	95	106	141	168	244	
85	8	11	18	25	34	56	79	140	199
96	7	10	16	23	32	53	74	131	186
100	12	15	19	28	34	56	78	135	184
107	8	11	16	22	32	52	73	131	186

b. Three per cent dispersion of Bentone 34-2HT-75

75	13	17	23	33	44	68	91	154	210
85	27	33	39	52	66	96	126	206	280
96	10	14	18	27	38	59	81	139	191
100	8	12	17	26	35	57	81	139	190
107	11	15	20	30	40	65	87	149	203

(Continued)

c. Three per cent dispersion of Bentone 38-2HT-75

meq. of Arquad added/100 g. of clay	Dial Deflection								
	3 r.p.m.	6 r.p.m.	11 r.p.m.	22 r.p.m.	33 r.p.m.	67 r.p.m.	100 r.p.m.	200 r.p.m.	300 r.p.m.
64	18	23	28	37	48	69	90	147	197
75	20	26	31	42	51	77	101	168	228
85	9	12	16	23	30	49	67	114	158
100	7	11	14	22	30	50	69	114	165
107	8	10	14	20	28	45	63	111	154

-57-

d. Two per cent dispersion of Bentone 45-2S-75^c

70	2	5	8	13	19	35	51	90	129
93	64	67	71	83	95	127	160	240	
100	53	55	61	70	81	110	142	220	291
116	8	10	15	24	32	52	74	130	176
140	10	12	16	24	28	56	80	138	185

a. All readings taken at 30 °C.

b. Time interval between readings was 15 seconds.

c. A 3% dispersion proved to be too viscous to read at 300 r.p.m.

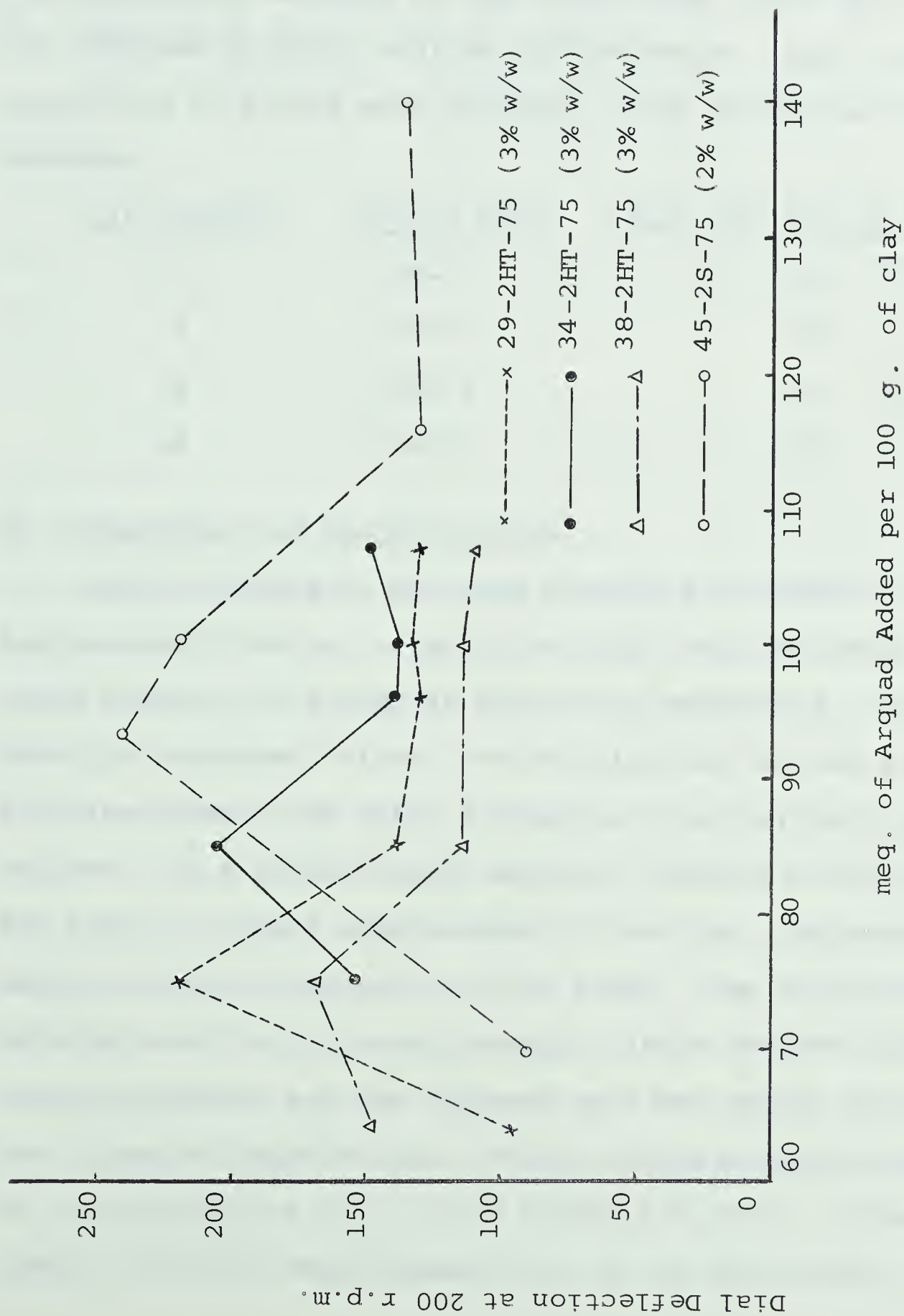


Fig. 4. Effect of Arquad-Bentonite Ratio on Gel Strength of Prepared Bentonites

In this way, it was found that the arquad ratio for bentonite sample 29 should be raised to 85 meq. for 100 gm. of clay when bentone 29-2HT-75 was being prepared on such a large scale. The quantities required by the other three clays were apparently not affected by this "scaling up" procedure. And the following quantities of Arquad were employed in the synthesis of the bentones.

<u>Clay Sample</u>	<u>Arquad Used</u>	<u>Meq. per 100 g. of clay</u>
29	2HT-75	85
34	2HT-75	85
38	2HT-75	75
45	2S-75	93

b) Preparation of Bentone Stocks

Using essentially the same procedure as detailed above, approximately two Kg. of purified clay, was mixed with the indicated quantity of Arquad as previously determined. To accommodate the increased volume, the reaction was carried out in a stainless steel tank using a propellor type variable speed power stirrer. As a precautionary measure, mixing was continued for two hours to ensure completeness of reaction. Adjustment of the amount of Arquad was made at this stage. The bulky flocculated material was then filtered through a large Buchner funnel under reduced pressure and the filtered cake was washed several times until free of chloride ion. Drying of the material was effected at low temperature (65°C) in a forced air oven. It was then passed through a swing hammer mill to 100 mesh powder and stored

in a closed container.

This procedure proved to be extremely tedious, requiring up to 20 hours to complete.

F. Rheological Properties of Bentonites

The cohesive forces between montmorillonite flakes is of relatively high order. These forces must necessarily be overcome in the process of swelling. This means that the swelling medium must penetrate between adjacent flakes and force them apart in order that a hull of liquid may form around each particle in the production of a gel.

Jordan and Williams (96) suggested that mechanical, thermal and chemical energies might be utilized to disperse organobentonite complexes in organic liquids. They claimed that chemical energy produced the most striking results. It was brought about by the addition of proportionately minor amounts of a highly polar compound to the relatively non-polar dispersing liquid.

In order to determine the influence of chemical and mechanical energies on the dispersing of a bentone in mineral oil, two series of tests were performed. Two bentones were selected for this study, Bentone 38 as the control and bentone 45-2S-75. The latter was chosen since it appeared to be the most promising of the complexes prepared from Alberta bentonites.

a) Effect of Alcohol Content (Polar Compound) on Gel Strength

Four grams of bentone was mixed with 192 to 196 grams of Marcol 70. High shear was obtained by employing a Waring Blendor

governed by a variable rheostat (Powerstat)*. After three minutes of mixing, the required weight of alcohol was added. Agitation was continued for an additional three minutes, after which the two per cent dispersion was transferred to the Fann viscometer. Readings were taken at 30°C for duplicate determinations.

For convenience, average up-curve values only are presented in Table IX. Data plotted in Fig. 5 are those obtained at 22 r.p.m. Individual values are recorded in Appendix Table II and III.

On examination of the data as plotted in Fig. 5, it was noted that gel strength in the 45-2S-75 series passed through a maximum at the one per cent (w/w) alcohol concentration. On the other hand, the Bentone 38 series appeared to increase in consistency throughout the range of alcohol concentrations employed. However, the steep slope at one per cent alcohol was considered indicative of the true value sought. This was later confirmed when it was observed that dispersions in this latter series containing more than one per cent of alcohol showed a distinct separation of alcohol in 24 hours.

* Type 500B, Standard Elect. Product Co., Dayton, Ohio, U.S.A.

TABLE IX

EFFECT OF ALCOHOL ON GEL STRENGTH OF BENTONE DISPERSIONS

a. Bentone 38

% w/w of Alcohol	Dial Deflection a, b, c, d										
	3 r.p.m.	2 r.p.m.	6 r.p.m.	11 r.p.m.	22 r.p.m.	33 r.p.m.	67 r.p.m.	100 r.p.m.	200 r.p.m.	300 r.p.m.	
0				3	5	9	15	29	43	86	119
0.5		14	15	24	27	36	58	78	134	181	
1.0	124		136	165	190	214	284				
1.5	162		175	206	238	268					
2.0	182		196	223	268						

b. Bentone 45-2S-75

0	2	3	5	10	15	28	44	83	123
0.5	38	40	46	56	70	98	125	196	260
1.0	82	84	90	100	114	156	198	300	
1.5	62	66	74	81	93	128	164	250	
2.0	56	58	64	72	84	116	147	226	296

a. Two per cent w/w dispersions in Marcol 70.

b. The average dial deflection readings of two determinations. Individual values are recorded in Appendix Table II and III.

c. All readings taken at 30°C.

d. Time interval between readings was 15 seconds.

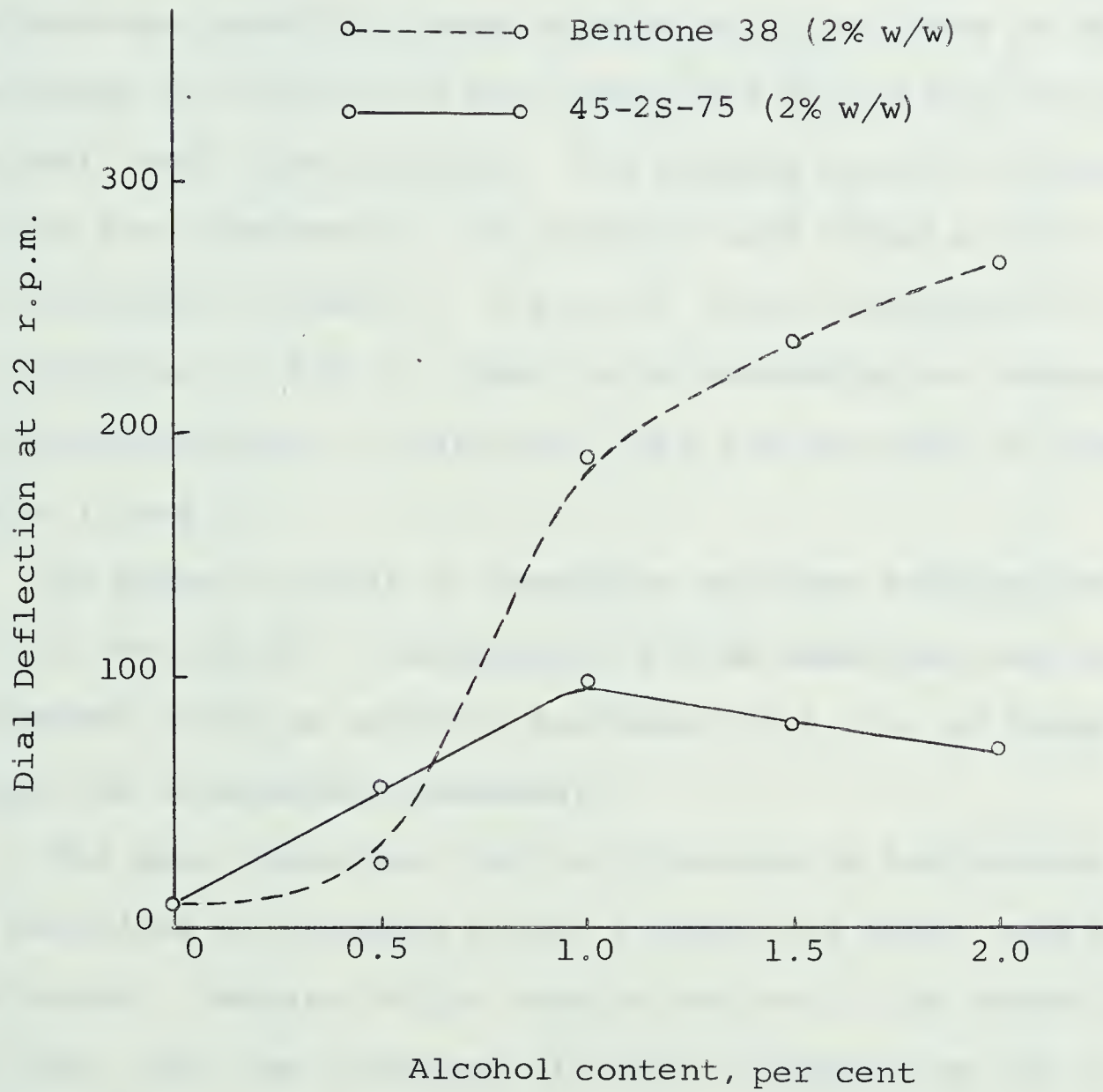


Fig. 5. Effect of Alcohol on Gel Strength of
Bentone Dispersions

b) Effect of Shear Rate on Gel Strength

As previously described, a Waring Blendor was connected to the power source through a Powerstat. Rotational speed was then controlled by means of the variable resistance dial of the latter instrument. In preparing the dispersions, four grams of bentone was mixed for three minutes with 194 grams of Marcol 70. Two grams of alcohol was then added and mixing was continued for an additional three minutes. The mixture was then transferred to the Fann Viscometer, and readings were taken at 30°C. Values are recorded in Table X. A plot of values obtained at 67 r.p.m. is presented in Fig. 6. Each value represents an average of two determinations. Individual data are recorded in Appendix Table IV and V.

As shown in Table X, Powerstat settings employed were 60, 70, 80, 90 and 100. Calibration of the powerstat was not attempted since an accurate knowledge of r.p.m. at these settings was considered unnecessary.

The data indicated that both Bentone 38 and bentone 45-2s-75 exhibited an increase in gel strength as shear rate was increased. Because of the complex nature of the system involved, the fact that the increases differed in degree was not unexpected.

However, it was shown that the consistency of the final product was a function of shear rate. Accordingly, in subsequent procedures involving the use of bentones in oil vehicles, maximum shear rates were employed wherever possible.

TABLE X

EFFECT OF SHEAR RATE ON GEL STRENGTH OF BENTONE DISPERSIONS

a. Bentone 38 (Control)

Powerstat Settings	Dial Deflection a, b, c, d									
	3 r.p.m.	6 r.p.m.	11 r.p.m.	22 r.p.m.	33 r.p.m.	67 r.p.m.	100 r.p.m.	200 r.p.m.	300 r.p.m.	
60	3	4	10	16	24	42	60	110	156	
70	19	22	33	38	50	76	101	168	230	
80	48	59	76	95	115	154	191	286		
90	104	112	125	151	172	227	290			
100	124	136	165	190	214	284				

b. Bentone 45-2S-75

60	14	17	26	34	43	63	86	145	197	
70	34	36	52	59	68	94	118	185	246	
80	48	52	70	78	88	118	148	216	282	
90	60	63	71	81	97	123	158	245		
100	82	84	90	100	114	156	198	-		

a. Two per cent w/w dispersions in Marcol 70, with 1% alcohol.

b. The average dial deflection readings of two determinations. Individual values are recorded in Appendix Table IV and V.

c. All readings taken at 30°C.

d. Time interval between readings was 15 seconds.

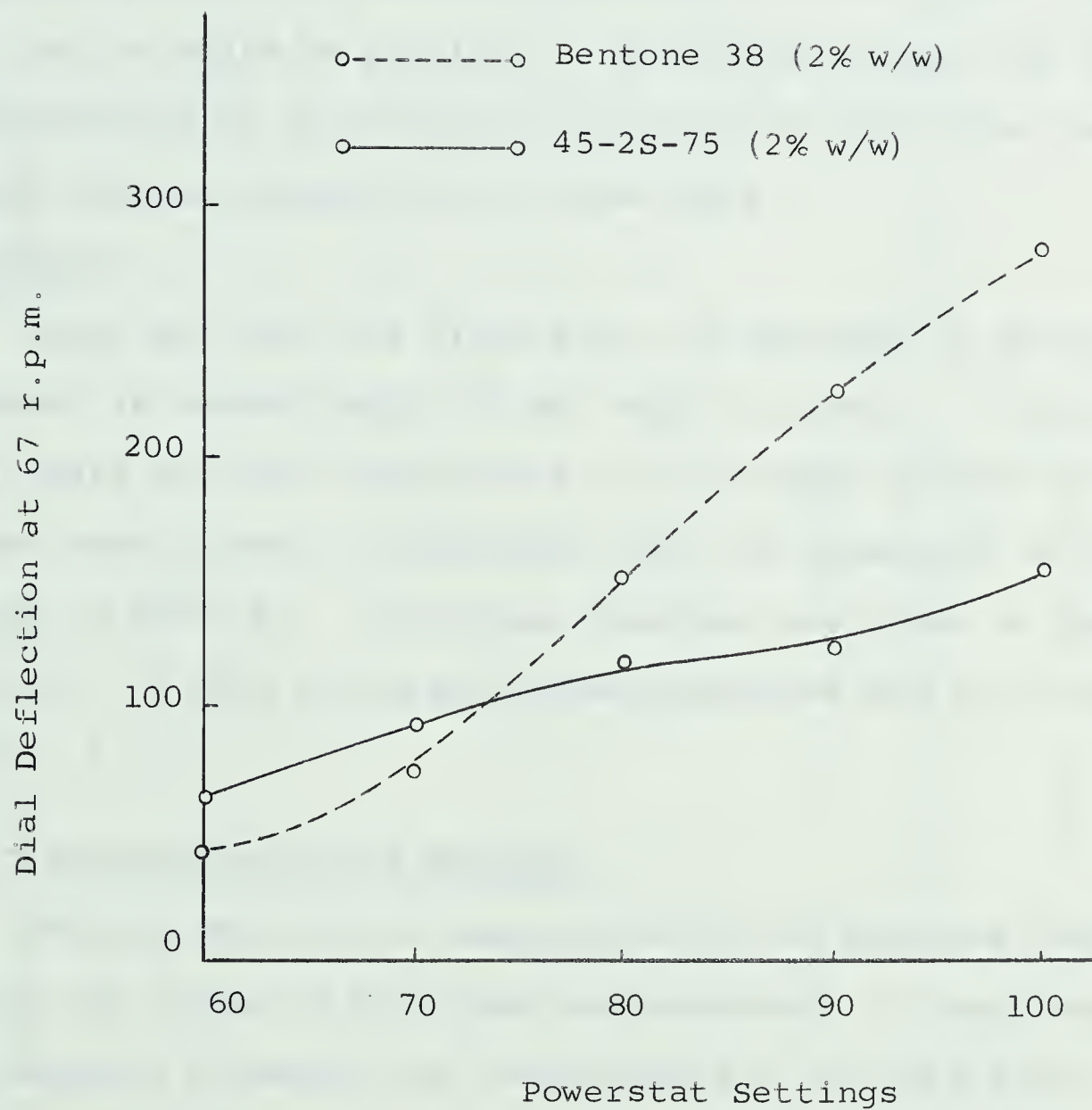


Fig. 6. Effect of Shear Rate on Gel
Strength of Bentonite Dispersions

c) Consistency of Bentone Samples

At an early stage in the investigation, rheograms were obtained from studies on the selected bentonite magmas. At that time, it was felt that it would be useful to run a similar series of determinations on bentones prepared from the same clays. In this way it would be possible to determine whether the relative consistencies as found for the clays would carry over unchanged to the bentone dispersions of those clays.

Procedure

Three per cent w/w dispersions of bentones in Marcol 70 were prepared as before using 1.5 per cent of alcohol. The viscometric data for each sample were then recorded at 30°C for both up and down curves, in duplicate, and are presented as average values in Table XI. Individual readings are shown in Appendix Table VI. A plot of these data was prepared and is illustrated in Fig. 7.

G. Characterization of Bentones

The desirability of characterizing the bentones prepared during the course of this work was examined. It was known that the accepted procedure for identification of clays such as bentonite required both differential thermal as well as x-ray data. Accordingly, attempts were made to obtain thermograms suitable for this purpose. Unfortunately, difficulties with the instrument were encountered, and satisfactory tracings were not obtained.

TABLE XI

DIAL DEFLECTION READINGS FOR 3 PER CENT BENTONE DISPERSIONS W/W
USING MODIFIED FANN VISCOMETER, $K_s = 62.4$, TEMPERATURE 30 °C

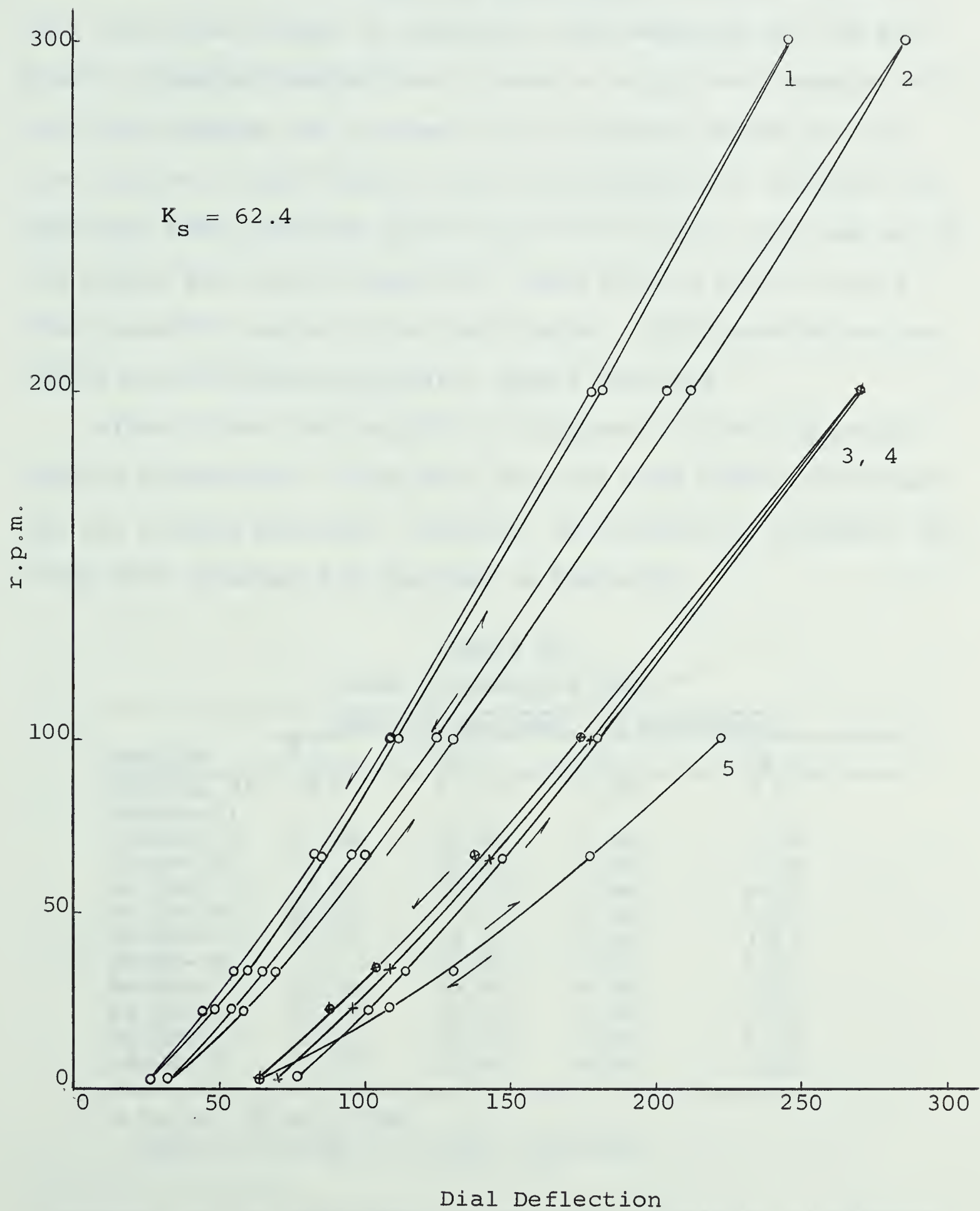
Bentone Sample	Dial Deflection a, b, c, d									
	3 r.p.m.	6 r.p.m.	11 r.p.m.	22 r.p.m.	33 r.p.m.	67 r.p.m.	100 r.p.m.	200 r.p.m.	300 r.p.m.	
38 (control)	64	73	86	108	131	178	222			
	64	72	86	106	130	178				
29-2HT-75	76	78	86	96	114	146	180	271		
	63	66	78	87	103	138	174			
34-2HT-75	32	36	46	57	69	100	130	212	286	
	32	35	44	54	64	95	125	204		
38-2HT-75	26	31	38	48	60	84	111	182	246	
	26	28	36	44	55	80	109	178		
45-2S-75	68	71	78	92	108	142	178	271		
	62	64	75	86	102	138	174			

- A 3% bentone in Marcol 70 with 1.5% alcohol.
- For each sample, the up-curve deflections are listed in the top line reading from left to right in ascending order. The down-curve deflections are listed in the bottom line reading from right to left in descending order.
- Time interval between readings was 15 seconds.
- Each value represents an average of the readings obtained from two different dispersions. For further details, see Appendix, Table VI.

FIGURE 7

CONSISTENCY CURVES OF BENTONE DISPERSIONS
3% W/W IN MARCOL 70 WITH 1.5% OF ALCOHOL

- | | | |
|---|--------------|---------|
| 1 | 38-2HT-75 | |
| 2 | 34-2HT-75 | |
| 3 | 45-2S-75 | x—————x |
| 4 | 29-2HT-75 | o—————o |
| 5 | 38 (Control) | |



Efforts to obtain x-ray data for a selected number of the samples were more successful. A Norelco x-ray diffractometer, with unfiltered copper K α radiation, was employed for the purpose*. Powdered samples were placed in a cylinder together with cellulose backing and pressed into a "biscuit" at 5000 psi for five minutes. Each biscuit was then subjected to radiation as mentioned above. The power source was 35 KV 15 MA. Scan was set at one degree per minute through 42° (from 3°2 θ to 45°2 θ) with a chart speed of one half inch per minute. The d-spacing on the charts was calibrated against a quartz standard.

Since it was not possible to complete the two characterization procedures, it was felt that the data were insufficient for the purpose proposed. However, as a matter of interest, the x-ray data obtained are recorded in Table XII.

TABLE XII
X-RAY DIFFRACTION DATA ^a

Samples	Lattice spacings, in Angstroms			
	d ₁	d ₂	d ₃	d ₄
Bentone 38 (control)	18.17	11.55	4.49	3.61
29-2HT-75	17.84	12.32	4.40	3.35
29-2S-75	-	13.59	4.46	3.35
34-2HT-75	18.49	12.29	4.44	4.03
34-2S-75	16.27	-	4.44	4.02
38-2HT-75	20.27	12.25	4.42	3.63
38-2S-75	-	13.31	4.43	4.02
44-2HT-75	19.06	12.02	4.41	3.61
44-2S-75	22.75	13.35	4.44	3.33
45-2HT-75	18.13	12.06	5.01	4.39
45-2S-75	21.08	13.47	4.45	3.82

a Cu K α , 35 KV 15 MA
Scan 42° (3°2 θ to 45°2 θ) 1°/minute

* Courtesy of the Department of Geology, University of Alberta

PART III FORMULATION AND EVALUATION OF BENTONE LOTIONS
AND OINTMENT BASES

A. Emulsified Lotion Bases

a) Formulation

Lotions were prepared using a modification of a formula as proposed by Billups for the preparation of Bentone ointment bases (97). The modified formula employed Marcol 70, bentone, alcohol, distilled water and Span 85*. This latter compound acted as a secondary emulsifier and helped to produce a more stable emulsion.

Preliminary testing indicated that a stable emulsion could not be obtained with Span 85 alone, even in concentrations as high as 10 per cent. Separation was observed in each case after 24 hours standing. However, when the bentone itself was employed in a concentration of 1.5 to 2 per cent, a stable but fairly coarse emulsion resulted. The addition of a small quantity of Span 85 was found to have a pronounced effect upon the emulsifying ability of the bentone, and it was therefore included in the formulation.

A series of specific studies were conducted to determine the optimum concentration of each ingredient necessary to form stable lotion bases with the synthesized bentones.

*Atlas Chemical Industries, Canada Ltd., Brantford, Ontario.
Sorbitan trioleate.

The following formula was found to produce the most satisfactory preparation.

Marcol 70	600 g .
Bentone	18 g .
Alcohol (95%)	9 g .
Span 85	13.5 g .
Distilled Water	560 g .

Procedure.

The oil and bentone were mixed in a Homo-Mixer* at high shear for five minutes. Alcohol was then added to the suspension. After two minutes of mixing, a thick, transparent brownish to greenish gel was formed. Span 85 was then incorporated into the gel and mixed for another two minutes. Finally, water was introduced, and the agitation was continued for an additional five minutes. A white to off-white lotion was formed.

For each of the five bentones involved, eight lots of 1,200 gm. of lotion were prepared. These were pooled to form a stock lotion. It was found that in the case of Bentone 38, a 1.5 per cent concentration produced a final lotion too thick to pour. Accordingly, it was found necessary to reduce the amount of Bentone 38 to one per cent in order to obtain a pourable lotion.

b) Evaluation of Bentone Lotions

On the basis of past experience, it was decided to employ shelf-testing at room temperature as the procedure of choice in evaluating the lotion bases. While tedious and time-consuming, it was felt that the data obtained would be more useful than

*Eppenbach Homo-Mixer distributed by Gifford-Wood Co., Hudson, N.Y.

data yielded by such procedures as accelerated testing at elevated temperatures.

Medicaments were chosen for incorporation into the lotion bases on the basis of their known utility and wide use in dermatology. In certain cases, well-known formulations were modified for study in this series.

Finished preparations, in triplicate, were transferred to 200 ml. clear glass prescription bottles, which had been previously calibrated. Each bottle was closed with a plastic screw-cap. Separation of clear oil on the surface of the lotion was determined by measuring the distance in mm. from the 200 ml. mark. Readings were taken at intervals, and the values were recorded as shown in Table XIII to XVII inclusive. Average values were then plotted against time, as presented in Fig. 8 to 20 inclusive.

Index of Medicated Bentone Lotions Prepared

- 1) Mercurous Chloride (Calomel), 0.9 per cent w/w.
- 2) Boric Acid, 5 per cent w/w.
- 3) Liquified Phenol, 2 per cent w/w.
- 4) Sulfur, Precipitated, 5 per cent w/w.
- 5) Zinc Oxide, 15 per cent w/w.
- 6) Burow's Solution, 5 per cent w/w.
- 7) Strong Lead Subacetate Solution, 10 per cent w/w.
- 8) Calamine Lotion, B. P. Modified.
- 9) Benzocaine, 2 per cent w/w.
- 10) Resorcinol, 10 per cent w/w.

*Solution of Aluminum Acetate, British Pharmaceutical Codex, 1963, The Pharmaceutical Press, London, England.

11) Coal Tar Solution, 10 per cent w/w.

Coal Tar Solution	80 g.
Span 85	16 g.
Bentone Vehicle, to make	800 g.

12) Menthol Compound (Rheumatic) Lotion.

Menthol	30 g.
Oil of Eucalyptus	54 ml.
Methyl Salicylate	244 ml.
Bentone Vehicle to make	650 g.

Procedure

Where possible, medicaments were simply added to the vehicle with high shear. In all cases, solids were ground to a fine powder prior to incorporation. Span 85 was used in lotion (11) to counteract the unusual thickening obtained with the bentone vehicle alone. It was felt that the excessive thickening was due to the high alcohol content of the Coal Tar Solution. The use of Span 85 was found to reverse this tendency and it was then possible to adjust the lotion to a proper consistency.

In preparing lotion (12), the relatively large volume of oily ingredients resulted in a product noticeably thinner than the others. Separation was observed in 24 hours.

A phase inversion was observed when calamine was incorporated into the 34-2HT-75 lotion base (lotion 8). However sufficient data were not available to explain this phenomenon.

TABLE XIII - SEPARATION OF OIL PHASE IN BENTONE LOTIONS a, b
1.0% Bentone 38 (Control)

Preparations	Time in Days													
	0	1	2	4	6	10	16	23	37	51	65	79	93	107
Blank	0	-	-	-	0	0	0	0.4	0.4	1.5	2.8	3.8	5.7	7.6
	0	-	-	-	0	0	0	0.4	0.4	1.4	2.6	2.6	5.2	7.0
	0	-	-	-	0	0	0	0	0.4	0.9	1.8	3.6	5.4	6.3
	0	-	-	-	0	0	0	0.3	0.4	1.3	2.4	3.3	5.4	7.0
Calomel	0	-	-	-	0	0	0	0.4	0.9	1.4	2.7	3.2	4.5	6.3
	0	-	-	-	0	0	0	0.4	0.4	0.9	1.8	2.7	3.6	6.3
	0	-	-	-	0	0	0	0.4	0.9	1.4	2.7	3.2	3.6	5.4
	0	-	-	-	0	0	0	0.4	0.7	1.2	2.4	3.0	3.9	6.0
Boric Acid	0	-	-	-	0	0	0	0.4	0.9	1.8	3.7	3.7	3.7	5.5
	0	-	-	-	0	0	0	0.4	0.9	1.4	2.7	2.7	3.6	5.4
	0	-	-	-	0	0	0	0.4	0.9	1.4	2.7	2.7	3.2	5.0
	0	-	-	-	0	0	0	0.4	0.9	1.5	3.0	3.0	3.5	5.3
Liq. Phenol	0	-	-	-	0	0.4	0.4	0.9	1.8	1.8	2.7	3.6	5.4	7.3
	0	-	-	-	0	0.2	0.4	0.9	1.4	1.7	2.6	3.6	5.2	7.0
	0	-	-	-	0	0.2	0.7	1.4	1.8	2.7	3.5	4.4	5.3	7.1
	0	-	-	-	0	0.3	0.5	1.1	1.7	2.1	2.9	3.9	5.3	7.1
Sulfur	0	-	-	-	0	0	0	0.9	1.8	1.8	3.6	4.5	5.4	8.2
	0	-	-	-	0	0	0	0.9	1.4	1.4	2.7	3.6	5.4	7.3
	0	-	-	-	0	0	0	0	0.9	1.4	2.7	3.6	5.4	7.3
	0	-	-	-	0	0	0	0.6	1.4	1.5	3.0	3.9	5.4	7.6
Zinc Oxide	0	-	-	-	1.8	1.8	3.5	4.4	5.3	6.2	7.1	8.8	11.5	13.3
	0	-	-	-	1.8	1.8	2.7	4.4	5.3	6.2	8.0	8.8	10.6	13.3
	0	-	-	-	0.9	1.8	1.8	4.6	5.5	6.4	8.3	9.2	12.0	13.9
	0	-	-	-	1.5	1.8	2.3	4.5	5.4	6.3	7.8	8.9	11.4	13.5
Burow's	0	-	-	-	0	0	0	0	0.2	0.2	0.2	0.4	0.4	0.9
	0	-	-	-	0	0	0	0	0.2	0.2	0.2	0.4	0.4	0.9
	0	-	-	-	0	0	0	0	0.2	0.2	0.2	0.4	0.4	0.9
	0	-	-	-	0	0	0	0	0.2	0.2	0.2	0.4	0.4	0.9

(Continued)

Preparations	Time in Days														
	0	1	2	4	6	10	16	23	37	51	65	79	93	107	
Lead Sub- acetate	0	-	-	-	0	0	0.9	1.8	2.7	3.6	4.0	4.5	5.4	6.3	
	0	-	-	-	0	0	0.9	1.8	2.7	3.6	4.0	4.5	5.4	5.8	
	0	-	-	-	0	0	0	0.9	1.8	2.7	3.3	3.6	4.5	5.0	
	0	-	-	-	0	0	0.6	1.5	2.4	3.3	3.8	4.2	5.1	5.7	
Calamine	0	-	0.9	-	-	3.8	4.7	5.6	7.5	9.4	11.2	14.0	15.0	16.9	
	0	-	0.9	-	-	3.6	3.6	5.4	7.3	9.1	10.9	12.7	15.4	17.3	
	0	-	0.9	-	-	2.7	3.6	4.5	6.3	7.3	10.9	13.6	15.4	18.2	
	0	-	0.9	-	-	3.4	4.0	5.2	7.0	8.6	11.0	13.4	15.3	17.5	
Benzocaine	0	-	-	-	0	0	0	0.4	0.9	1.8	3.7	4.6	5.5	7.4	
	0	-	-	-	0	0	0	0.4	0.9	1.8	3.6	5.4	7.3	9.1	
	0	-	-	-	0	0	0	0.4	0.9	1.4	2.7	4.5	5.4	6.3	
	0	-	-	-	0	0	0	0.4	0.9	1.7	3.3	4.8	6.7	7.6	
Resorcinol	0	-	-	-	0	0	0	0.9	3.6	4.5	5.4	6.3	7.3	9.1	
	0	-	-	-	0	0	0	0.9	1.8	1.8	1.8	2.7	2.7	4.4	
	0	-	-	-	0	0	0	0.9	1.8	1.8	1.8	2.7	2.7	4.4	
	0	-	-	-	0	0	0	0.9	2.4	2.7	3.0	3.9	4.2	6.0	
Coal Tar	0	-	-	-	0	0	0	0.4	1.8	2.7	4.5	6.3	7.3	10.0	
	0	-	-	-	0	0	0.4	0.9	2.7	3.5	4.4	5.3	7.1	9.7	
	0	-	-	-	0	0	0	0.4	2.7	3.3	5.4	6.3	8.2	10.9	
	0	-	-	-	0	0	0.1	0.6	2.4	3.2	4.8	6.0	7.5	10.2	
Menthol ^c Compound	0	25.3	48.1	58.6	67.4	72.7	72.7	74.4	74.4	74.4	74.4	74.4	74.4	74.4	
	0	28.8	55.3	67.4	70.9	76.2	76.2	76.2	76.2	76.2	76.2	76.2	76.2	76.2	
	0	28.8	58.6	62.1	67.4	72.7	74.4	86.2	76.2	76.2	76.2	76.2	76.2	80.0	
	0	27.6	54.0	62.7	68.6	73.9	74.4	75.6	75.6	75.6	75.6	75.6	75.6	76.9	

a. Values in Table represent supernatant oil phase in ml.

b. The underlined values represent the average.

c. Values represent creaming of the emulsion in ml.

TABLE XIV - SEPARATION OF OIL PHASE IN BENTONE LOTIONS a, b
1.5% bentone 29-2HT-75

Preparations	Time in Days													
	0	2	5	11	13	15	19	25	32	46	60	74	88	102
Blank	0	0	-	2.7	-	-	6.3	6.3	7.3	9.1	10.0	11.8	13.6	14.5
	0	0	-	3.0	-	-	5.0	7.0	8.0	9.0	11.0	13.0	15.0	18.0
	0	0	-	3.4	-	-	6.0	6.8	7.7	9.4	10.3	11.2	13.7	15.4
	0	0	-	3.0	-	-	5.8	6.8	7.7	9.2	10.4	12.0	14.1	16.0
Calomel	0	0	-	3.8	-	-	6.5	7.5	7.5	9.4	10.3	12.1	13.1	14.0
	0	0	-	2.8	-	-	5.6	6.5	7.5	8.4	11.2	12.1	13.1	15.0
	0	0	-	2.8	-	-	4.7	5.6	7.5	8.4	10.3	12.1	13.1	15.9
	0	0	-	3.1	-	-	5.6	6.5	7.5	8.7	10.6	12.1	13.1	15.0
Boric Acid	0	0.9	-	3.6	-	-	6.3	7.3	7.3	9.1	10.9	12.7	13.6	14.5
	0	0.9	-	3.8	-	-	4.7	4.7	5.6	7.5	10.3	12.1	13.1	15.0
	0	0.9	-	1.8	-	-	5.4	5.4	6.3	8.2	10.0	12.7	14.5	16.4
	0	0.9	-	3.1	-	-	5.5	5.8	6.4	8.3	10.4	12.5	13.4	15.3
Liq. Phenol	0	0	-	1.9	-	-	2.8	3.8	3.8	3.8	5.6	5.6	6.5	7.5
	0	0	-	1.8	-	-	1.8	2.8	2.8	3.7	5.5	5.5	5.5	6.4
	0	0	-	0.9	-	-	1.9	2.8	2.8	3.4	4.7	5.6	5.6	6.5
	0	0	-	1.2	-	-	2.2	3.1	3.1	3.6	5.3	5.6	5.9	6.8
Sulfur	0	0.9	-	4.4	-	-	5.3	5.3	6.2	8.8	10.6	12.4	13.3	15.9
	0	0.9	-	2.7	-	-	5.3	5.3	6.2	8.0	9.7	11.5	12.4	15.0
	0	0.9	-	2.6	-	-	4.4	4.4	5.2	7.0	10.4	12.2	13.1	15.7
	0	0.9	-	3.2	-	-	5.0	5.0	5.7	7.9	10.2	12.0	12.9	15.5
Zinc Oxide	0	0.9	-	3.7	-	-	3.7	3.7	5.5	6.4	6.4	7.4	11.0	13.0
	0	0.9	-	2.7	-	-	3.6	3.6	4.5	6.3	7.3	8.2	10.9	12.7
	0	0.9	-	1.8	-	-	3.5	3.5	4.4	5.3	6.2	7.1	10.6	12.4
	0	0.9	-	2.7	-	-	3.6	3.6	4.8	6.0	6.6	7.6	10.8	12.7
Burow's	0	0	-	1.9	-	-	4.7	4.7	5.6	7.5	9.4	12.1	12.1	13.1
	0	0	-	0.9	-	-	3.7	3.7	4.6	6.4	9.2	11.1	11.1	13.0
	0	0	-	0.9	-	-	2.7	3.6	4.5	6.3	8.2	9.1	10.9	11.8
	0	0	-	1.2	-	-	3.7	4.0	4.9	6.7	8.9	10.8	11.4	12.6

(Continued)

Preparations	Time in Days													
	0	2	5	11	13	15	19	25	32	46	60	74	88	102
Lead Sub- acetate	0	0.9	-	2.7	-	-	4.5	4.5	4.5	8.2	9.1	10.0	11.8	13.6
	0	0.9	-	2.7	-	-	3.6	4.5	4.5	5.4	7.3	8.2	10.5	11.8
	0	0.9	-	3.7	-	-	5.5	5.5	5.5	7.4	7.8	9.2	12.0	13.9
	0	0.9	-	3.0	-	-	4.5	4.8	4.8	7.0	8.1	9.1	11.4	13.1
Calamine	0	0.9	-	4.7	-	-	5.6	5.6	7.5	8.4	10.3	12.1	14.0	15.0
	0	0.9	-	4.7	-	-	6.5	6.5	8.4	8.4	12.1	13.1	15.0	15.9
	0	0.9	-	4.4	-	-	5.3	6.2	8.0	8.0	10.6	11.5	13.3	15.0
	0	0.9	-	4.6	-	-	5.8	6.1	8.0	8.3	11.0	12.2	13.1	15.3
Benzocaine	0	1.0	-	3.0	-	-	3.9	3.9	3.9	4.9	6.9	6.9	6.9	7.5
	0	0.9	-	2.8	-	-	3.8	3.8	3.8	3.8	5.6	6.6	6.5	7.5
	0	0.9	-	2.8	-	-	3.7	3.7	3.7	4.6	6.4	6.4	6.4	7.4
	0	0.9	-	2.9	-	-	3.8	3.8	3.8	4.4	6.3	6.6	6.6	7.5
Resorcinol	0	0.9	-	3.8	-	-	4.7	4.7	5.6	6.5	7.5	9.4	9.4	10.3
	0	9.9	-	3.8	-	-	4.7	5.6	6.5	7.5	10.3	11.2	11.2	13.1
	0	0	-	1.8	-	-	2.7	3.6	4.5	5.0	7.3	9.1	9.1	10.0
	0	0.6	-	3.1	-	-	4.0	4.6	5.5	6.3	8.3	9.9	9.9	11.1
Coal Tar	0	0	-	1.8	-	-	2.7	2.7	3.2	4.4	4.9	6.2	7.1	7.1
	0	0	-	0.9	-	-	1.8	1.8	2.2	2.7	3.2	4.0	5.0	5.8
	0	0	-	0.9	-	-	1.8	1.8	2.2	2.2	3.6	4.5	5.0	5.8
	0	0	-	1.2	-	-	2.4	2.4	2.5	3.1	3.9	4.9	5.7	6.2
Menthol ^c Compound	0	15.1	28.8	37.6	39.4	41.2	46.5	50.7	53.4	63.9	67.4	70.9	74.4	76.2
	0	11.7	23.5	34.1	37.6	39.4	44.8	48.1	53.4	58.6	62.1	65.6	69.2	72.7
	0	14.5	28.8	35.9	39.4	43.0	46.5	50.7	52.5	57.1	60.4	62.1	67.4	72.7
	0	13.7	27.0	35.9	38.8	41.2	45.9	49.8	53.1	59.8	63.3	66.2	70.3	73.9

a. Values in Table represent supernatant oil phase in ml.

b. The underlined values represent the average.

c. Values represent creaming of the emulsion in ml.

TABLE XV - SEPARATION OF OIL PHASE IN BENTONE LOTIONS a, b

1.5% bentone 34-2HT-75

Preparations	Time in Days										
	0	1	3	7	13	20	34	48	62	76	90
Blank	0	-	-	0	0	0.4	0.9	0.9	1.7	2.6	4.4
	0	-	-	0	0	0	0.2	0.4	0.9	2.7	4.5
	0	-	-	0	0	0	0.2	0.4	0.9	2.7	4.5
	0	-	-	0	0	0.1	0.4	0.6	1.2	2.7	4.5
Calomel	0	-	-	0	0	0	0.2	0.2	0.9	0.9	2.8
	0	-	-	0	0	0.4	0.6	0.6	0.9	1.5	2.8
	0	-	-	0	0	0	0.2	0.2	0.4	0.9	1.8
	0	-	-	0	0	0.1	0.3	0.3	0.7	1.1	2.5
Boric Acid	0	-	-	0	0.4	0.9	2.1	2.7	2.7	3.6	3.6
	0	-	-	0	0.9	1.3	2.8	3.7	4.6	5.5	7.4
	0	-	-	0	0.4	1.0	2.0	3.0	4.0	5.0	7.0
	0	-	-	0	0.6	1.1	2.3	3.1	3.8	4.7	6.0
Liq. Phenol	0	-	-	1.8	1.8	2.4	4.1	6.4	7.4	10.2	13.0
	0	-	-	0.9	1.8	2.8	3.7	6.4	7.4	10.2	13.0
	0	-	-	1.7	1.7	2.0	3.4	5.1	6.0	8.6	11.2
	0	-	-	1.5	1.8	2.4	3.7	6.0	6.9	9.7	12.4
Sulfur	0	-	-	0	0	0.2	0.2	0.8	1.7	1.7	2.6
	0	-	-	0	0	0.2	0.5	0.8	2.0	3.4	4.3
	0	-	-	0	0	0.2	0.4	0.4	1.0	1.9	3.8
	0	-	-	0	0	0.2	0.4	0.7	1.6	2.3	3.6
Zinc Oxide	0	-	-	2.6	3.1	3.4	4.3	5.1	6.8	8.6	11.2
	0	-	-	1.7	2.5	3.3	4.7	5.8	7.5	8.3	11.7
	0	-	-	1.7	2.6	3.4	4.3	5.1	6.8	8.6	11.2
	0	-	-	2.0	2.7	3.4	4.4	5.3	7.0	8.5	11.4
Burow's	0	-	-	0	0	0.2	0.4	0.4	0.4	0.9	1.5
	0	-	-	0	0	0.2	0.2	0.4	0.4	0.9	1.5
	0	-	-	0	0	0.2	0.2	0.4	0.4	0.9	1.4
	0	-	-	0	0	0.2	0.3	0.4	0.4	0.9	1.5

(Continued)

Preparations	Time in Days											
	0	1	3	7	13	20	34	48	62	76	90	104
Lead Sub- acetate	0	-	-	0.9	1.8	3.6	4.5	7.2	8.1	9.0	12.5	13.4
	0	-	-	0.8	1.7	2.5	5.0	7.5	8.3	10.0	12.5	13.3
	0	-	-	0.8	1.7	2.5	4.2	6.7	7.5	9.2	11.7	11.7
	0	-	-	0.8	1.7	2.9	4.6	7.1	8.0	9.4	12.2	12.8
Calamine ^d	0	16.4	23.6	23.6	25.4	25.4	25.4	25.4	25.4	27.3	27.3	28.2
	0	14.5	20.0	20.0	21.8	21.8	25.4	25.4	25.4	27.3	27.3	27.3
	0	14.1	21.2	21.2	23.0	23.0	24.8	24.8	24.8	24.8	24.8	26.5
	0	15.0	21.6	21.6	23.4	23.4	25.2	25.2	25.2	26.5	26.5	27.3
Benzoacaine	0	-	-	0.9	3.7	3.7	5.5	8.3	11.1	12.0	15.7	16.6
	0	-	-	0	3.7	3.7	5.5	8.3	9.2	13.0	15.7	16.6
	0	-	-	0	1.8	2.8	3.7	7.4	8.3	10.2	13.9	16.6
	0	-	-	0.3	3.1	3.4	4.9	8.0	9.5	11.7	15.1	16.6
Resorcinol	0	-	-	1.8	2.8	3.7	5.5	5.5	5.5	7.4	8.3	8.3
	0	-	-	0.8	1.7	2.5	4.2	5.0	5.0	5.8	6.7	6.7
	0	-	-	1.8	2.8	3.7	5.5	6.4	6.4	7.4	7.4	8.3
	0	-	-	1.5	2.4	3.3	5.1	5.6	5.6	6.9	7.5	7.8
Coal Tar	0	-	-	0	0.4	1.0	1.5	2.3	2.8	3.8	6.6	6.6
	0	-	-	0	0.4	0.9	1.4	2.2	2.7	3.6	6.3	6.3
	0	-	-	0	0.4	0.9	1.4	2.2	2.7	3.6	5.4	5.8
	0	-	-	0	0.4	0.9	1.4	2.2	2.7	3.7	6.1	6.2
Menthol Compound ^c	0	14.5	25.0	35.0	38.3	45.0	50.0	58.3	66.7	71.7	75.0	76.7
	0	16.3	28.5	40.9	44.7	50.0	55.4	57.2	61.7	64.4	69.8	73.4
	0	8.2	21.7	33.3	38.3	40.0	46.7	53.3	55.0	60.8	63.3	63.3
	0	13.0	25.1	36.4	40.4	45.0	50.7	56.3	61.1	65.6	69.4	71.1

a. Values in Table represent supernatant oil phase in ml.

b. The underlined values represent the average.

c. Values represent creaming of the emulsion in ml.

d. Values represent supernatant water phase in ml.

TABLE XVI - SEPARATION OF OIL PHASE IN BENTONE LOTIONS a, b
1.5% bentone 38-2HT-75

Preparations	Time in Days										
	0	1	3	6	15	23	29	36	50	64	92
Blank	0	-	-	0	0	2.7	3.6	4.5	5.4	5.4	7.3
	0	-	-	0	1.7	4.4	5.2	5.2	6.1	8.7	8.2
	0	-	-	0	0.9	3.6	4.5	4.5	5.4	6.3	11.3
	0	-	-	0	0.9	3.6	4.4	4.7	5.6	6.8	9.1
	0	-	-	0	0.9	3.6	4.4	4.7	5.6	6.8	9.5
Calomel	0	-	-	0.9	3.6	4.5	4.5	4.5	5.4	6.3	9.9
	0	-	-	0.9	2.8	3.8	3.8	3.8	3.8	4.7	8.4
	0	-	-	0.9	3.4	4.3	4.3	4.3	4.3	5.1	8.6
	0	-	-	0.9	3.3	4.2	4.2	4.2	4.5	5.4	9.0
Boric Acid	0	-	-	1.9	2.8	3.8	4.7	5.6	7.5	8.4	15.9
	0	-	-	1.8	2.7	3.5	4.4	5.3	6.2	7.1	13.3
	0	-	-	1.9	2.8	3.8	4.8	5.7	5.7	8.6	12.4
	0	-	-	1.9	2.8	3.7	4.6	5.5	6.5	8.0	13.9
Phenol	0	-	-	0.9	3.8	3.8	3.8	3.8	4.2	4.2	6.5
	0	-	-	0.9	1.8	2.7	2.7	2.7	3.2	3.5	7.1
	0	-	-	0.9	1.8	2.7	2.7	3.6	3.6	4.0	7.2
	0	-	-	0.9	2.5	3.1	3.1	3.4	3.7	3.9	7.3
Sulfur	0	-	-	0.9	3.5	3.5	3.5	4.4	6.2	8.0	13.3
	0	-	-	0	2.0	3.0	4.0	4.0	6.0	7.0	14.0
	0	-	-	0	1.8	3.5	3.5	3.5	5.3	7.1	12.4
	0	-	-	0.3	2.4	3.3	3.7	4.0	5.8	7.4	13.2
Zinc Oxide	0	1.0	1.9	3.8	6.6	-	6.6	6.6	9.5	14.2	16.2
	0	0.9	1.9	3.8	7.5	-	8.4	8.4	10.3	15.0	19.7
	0	1.0	1.9	3.8	7.6	-	8.6	8.6	10.4	14.2	19.0
	0	1.0	1.9	3.8	7.2	-	7.9	7.9	10.1	14.5	18.3
Burow's	0	-	-	0	0.9	3.8	4.8	6.6	6.6	6.6	10.4
	0	-	-	0	0	1.9	3.8	4.7	5.6	6.0	10.3
	0	-	-	0	0	1.9	2.8	3.8	5.6	6.0	7.5
	0	-	-	0	0.3	2.5	3.8	5.0	5.9	6.2	8.2
	0	-	-	0	0.3	2.5	3.8	5.0	5.9	6.2	9.7

(Continued)

Preparations	Time in Days												
	0	1	3	6	15	23	29	36	50	64	78	92	106
Lead Sub- acetate	0	-	0	3.8	7.5	7.5	7.5	7.5	10.3	11.3	15.0	16.9	18.8
	0	-	0.9	3.6	7.2	8.1	8.1	8.1	9.9	10.8	14.4	15.2	16.1
	0	-	0.9	3.7	9.2	10.2	10.2	10.2	12.0	12.0	14.8	15.7	17.5
	0	-	0.6	3.7	8.0	8.6	8.6	8.6	10.7	11.3	14.7	15.9	17.5
Calamine	0	1.9	3.8	5.4	7.5	9.4	9.4	10.3	12.1	15.9	18.8	21.6	23.4
	0	2.7	3.6	5.4	6.3	8.1	9.0	10.8	12.5	15.2	18.8	20.6	23.3
	0	1.8	3.5	5.3	6.2	8.0	8.8	10.6	13.3	15.9	18.5	21.2	23.9
	0	2.1	3.6	5.4	6.7	8.5	9.1	10.6	12.6	15.7	18.7	21.1	23.5
Benzocaine	0	-	-	0.9	3.6	3.6	4.5	4.5	6.3	8.1	10.8	12.5	12.5
	0	-	-	0	1.8	2.7	3.6	3.6	4.5	6.3	9.0	9.9	11.7
	0	-	-	0	1.7	1.7	2.6	2.6	3.4	5.1	7.7	9.4	12.0
	0	-	-	0.3	2.4	2.7	3.6	3.6	4.7	6.5	9.2	10.6	12.1
Resorcinol	0	-	-	1.8	2.7	2.7	2.7	3.2	3.9	3.9	6.2	7.1	8.8
	0	-	-	1.9	2.8	2.8	2.8	3.4	3.4	3.4	5.6	6.5	7.5
	0	-	-	1.7	2.6	2.6	2.6	3.1	3.1	3.4	5.1	6.0	6.8
	0	-	-	1.8	2.7	2.7	2.7	3.2	3.5	3.6	5.6	6.5	7.7
Coal Tar	0	-	0.9	2.6	3.5	5.2	5.2	5.2	6.1	8.7	11.3	13.1	14.8
	0	-	0	1.8	2.7	5.4	5.4	5.4	6.3	7.3	10.8	11.7	14.3
	0	-	0.9	2.8	3.7	4.6	4.6	4.6	7.4	8.3	9.2	10.2	12.0
	0	-	0.6	2.4	3.3	5.1	5.1	5.1	6.6	8.1	10.4	11.7	13.4
Menthol ^c Compound	0	27.3	38.2	52.7	56.4	60.0	61.8	63.6	65.2	69.1	70.9	76.4	81.8
	0	30.6	46.5	55.3	58.6	62.1	63.9	65.6	65.6	65.6	65.6	65.6	69.2
	0	25.3	46.5	55.3	62.1	62.1	63.9	63.9	63.9	63.9	63.9	63.9	69.2
	0	27.7	43.4	54.4	59.0	61.4	63.2	64.3	64.9	66.2	66.7	68.6	73.4

a. Values in Table represent supernatant oil phase in ml.

b. The underlined values represent the average.

c. Values represent creaming of the emulsion in ml.

TABLE XVII - SEPARATION OF OIL PHASE IN BENTONE LOTIONS a, b
1.5% bentone 45-2S-75

Preparations	Time in Days											
	0	2	4	8	14	21	35	49	63	77	91	105
Blank	0	-	-	0	0	0.4	0.9	2.7	2.7	3.6	3.6	3.6
	0	-	-	0	0	0	0.4	0.9	0.9	1.5	1.5	1.5
	0	-	-	0	0	0	0.2	0.9	0.9	1.8	1.8	2.2
	0	-	-	0	0	0.1	0.5	1.5	1.5	2.3	2.3	2.8
Calomel	0	-	-	0	0	0.4	0.5	0.9	2.6	3.5	4.0	4.0
	0	-	-	0	0	0	0.2	0.5	1.4	1.8	1.8	1.8
	0	-	-	0	0	0	0	0.5	1.4	1.7	1.7	1.7
	0	-	-	0	0	0.1	0.3	0.6	1.8	2.3	2.5	2.5
Boric Acid	0	-	-	0	0.4	0.9	1.4	1.8	2.1	3.5	4.0	5.3
	0	-	-	0	0.4	0.9	1.4	2.1	2.7	3.6	4.5	5.4
	0	-	-	0	0.4	0.9	1.8	2.2	2.8	4.5	5.4	6.3
	0	-	-	0	0.4	0.9	1.5	2.0	2.5	3.9	4.6	5.7
Phenol	0	-	-	0	0.4	0.9	1.8	2.2	2.7	2.8	3.2	4.2
	0	-	-	0	0.4	0.9	1.4	1.8	2.1	2.7	2.7	3.6
	0	-	-	0	0.4	0.9	1.8	2.2	2.7	2.8	3.2	4.0
	0	-	-	0	0.4	0.9	1.7	2.3	2.5	2.8	3.0	3.9
Sulfur	0	-	-	0	0	0.2	0.5	0.9	3.6	3.6	4.0	4.5
	0	-	-	0	0	0.2	0.5	0.9	1.4	1.8	2.7	3.1
	0	-	-	0	0	0.2	0.9	0.9	1.8	1.8	2.2	2.7
	0	-	-	0	0	0.2	0.7	0.9	2.3	2.4	3.0	3.4
Zinc Oxide	0	-	-	0.9	0.9	1.9	2.4	2.4	2.8	2.8	4.7	5.6
	0	-	-	0	0.4	0.9	1.8	2.2	2.7	3.6	5.4	7.2
	0	-	-	0	0.4	0.9	1.4	2.2	2.7	3.6	5.4	7.3
	0	-	-	0.3	0.6	1.2	1.9	2.3	2.7	3.3	5.2	6.7
Burow's	0	-	-	0	0	0	0.2	0.4	0.9	0.9	1.4	1.8
	0	-	-	0	0	0	0.2	0.4	0.5	0.9	0.9	1.4
	0	-	-	0	0	0	0.2	0.5	0.5	0.9	1.4	1.8
	0	-	-	0	0	0	0.2	0.4	0.7	0.9	1.2	1.7

(Continued)

Preparations	Time in Days											
	0	2	4	8	14	21	35	49	63	77	91	105
Lead Sub- acetate	0	-	-	3.6	4.5	4.5	7.2	8.0	9.1	10.0	10.9	10.9
	0	-	-	2.8	4.7	5.6	7.5	8.4	9.4	10.3	11.2	11.2
	0	-	-	2.7	3.6	4.5	6.3	7.2	7.9	9.0	10.7	10.7
	0	-	-	3.0	4.3	4.9	7.0	7.9	8.8	9.8	10.9	10.9
Calamine	0	-	-	3.3	5.0	5.8	7.5	9.2	10.8	13.3	15.0	15.3
	0	-	-	3.5	5.2	6.0	8.5	9.5	12.0	13.0	15.6	17.0
	0	-	-	4.0	5.0	6.0	9.0	10.0	12.0	14.0	17.0	18.0
	0	-	-	3.6	5.1	5.9	8.3	9.6	11.6	13.4	15.8	16.9
Benzoacaine	0	-	-	0.9	0.9	1.8	2.7	3.2	4.5	5.4	6.3	6.9
	0	-	-	0	0.9	1.8	2.3	3.2	4.5	5.8	7.3	9.1
	0	-	-	0	0.9	1.8	2.7	3.2	4.4	6.2	8.0	10.2
	0	-	-	0.3	0.9	1.8	2.6	3.2	4.5	5.8	7.2	8.7
Resorcinol	0	-	-	0.9	0.9	1.8	2.7	3.6	4.5	5.0	5.8	6.9
	0	-	-	0.9	0.9	1.8	2.7	3.5	4.4	4.9	6.2	6.7
	0	-	-	0.9	0.9	2.2	2.8	3.7	4.6	5.2	5.9	7.4
	0	-	-	0.9	0.9	1.9	2.7	3.6	4.5	5.0	6.0	7.0
Coal Tar	0	-	-	0.9	0.9	0.9	2.2	2.7	3.6	4.5	5.0	6.5
	0	-	-	0.9	0.9	0.9	2.7	2.7	4.5	4.5	4.5	5.4
	0	-	-	0.9	0.9	0.9	1.8	2.7	3.6	4.5	4.5	5.4
	0	-	-	0.9	0.9	0.9	2.2	2.7	3.9	4.5	4.7	5.7
Menthol Compound ^c	0	0	3.3	5.0	10.0	20.0	33.6	38.2	45.4	49.1	52.7	52.7
	0	0	1.8	5.5	11.8	20.0	27.7	32.0	39.7	42.3	45.7	47.4
	0	0	1.8	5.5	12.7	20.0	28.8	34.1	37.6	41.2	44.8	44.8
	0	0	2.3	5.3	11.5	20.0	30.0	34.8	40.9	44.2	47.7	48.3

a. Values in Table represent supernatant oil phase in ml.

b. The underlined values represent the average

c. Values represent creaming of the emulsion in ml.

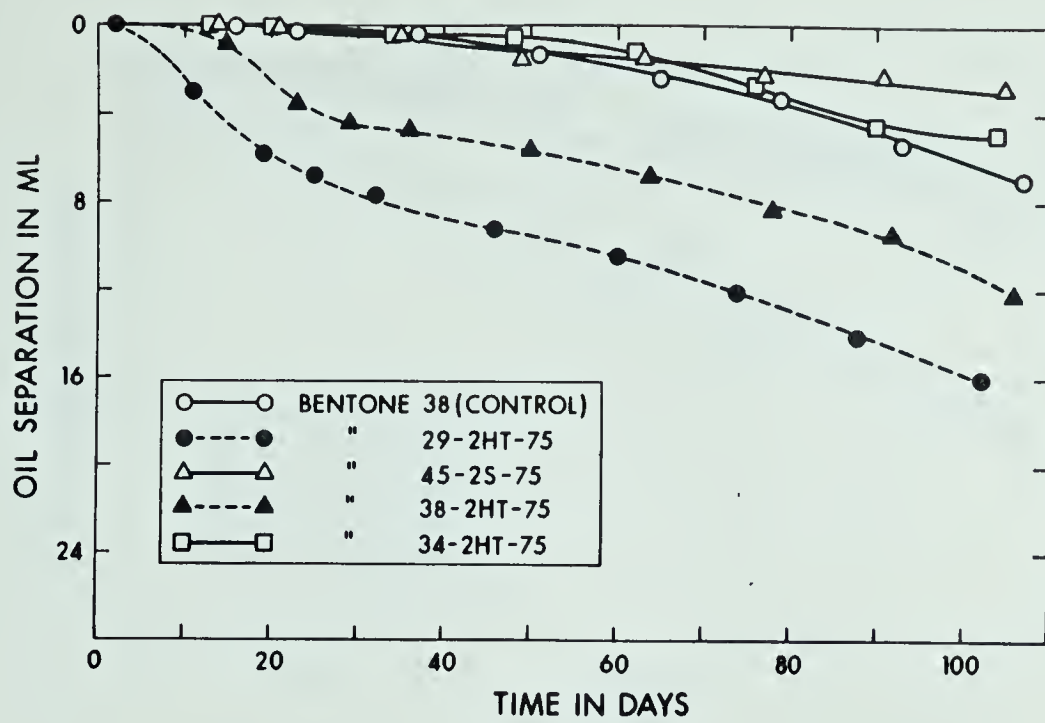


Fig. 8. Stability of Bentone Lotion Bases.

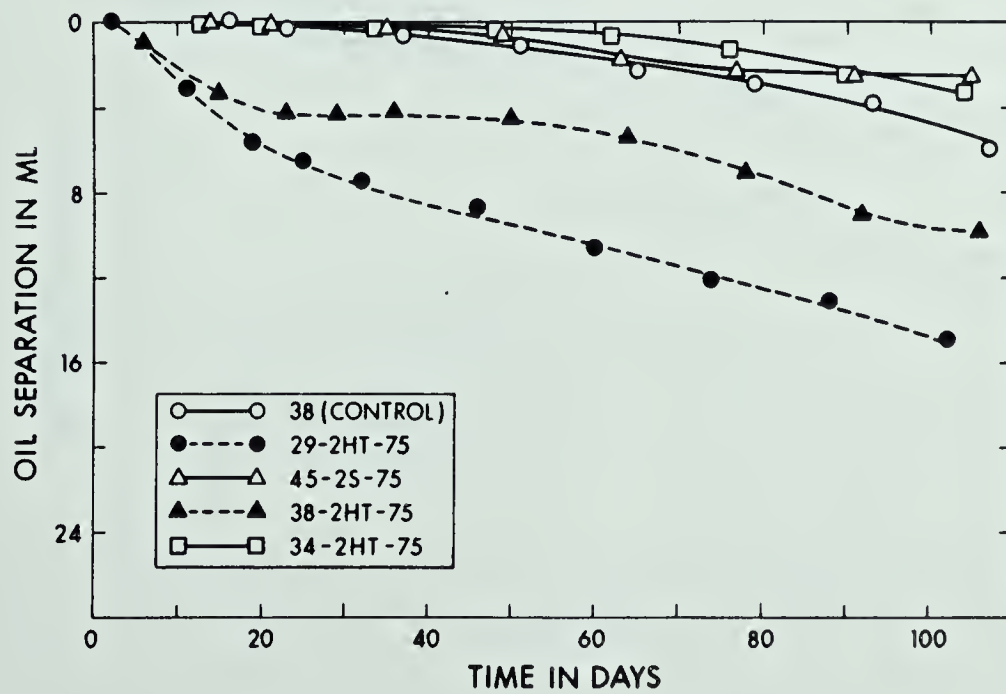


Fig. 9. Stability of Bentone Lotion Bases with Calomel.

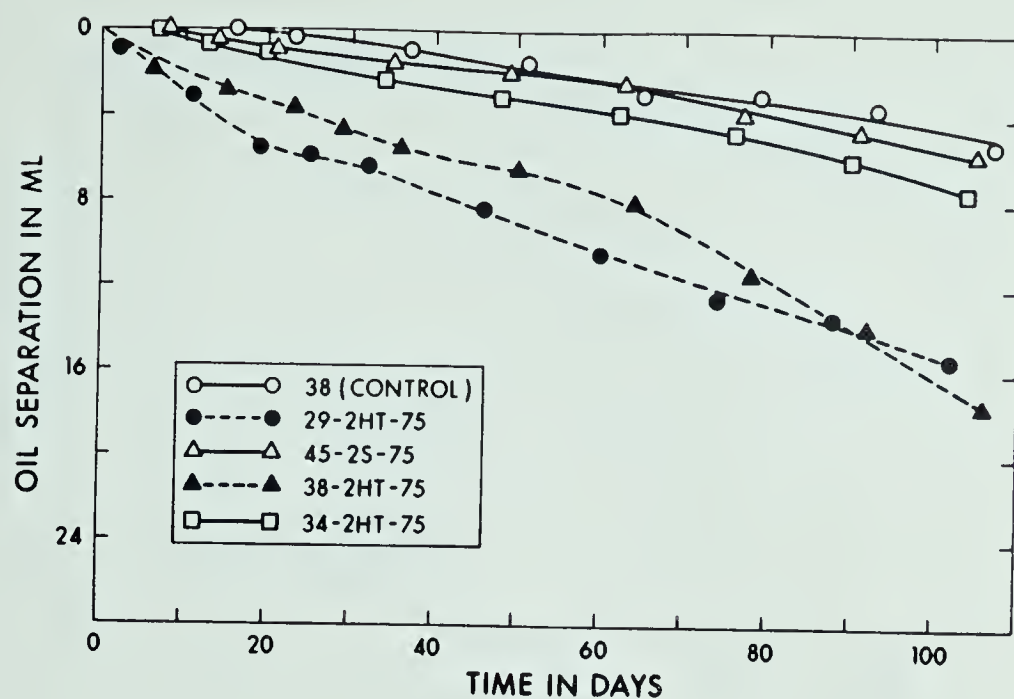


Fig. 10. Stability of Bentone Lotion Bases with Boric Acid.

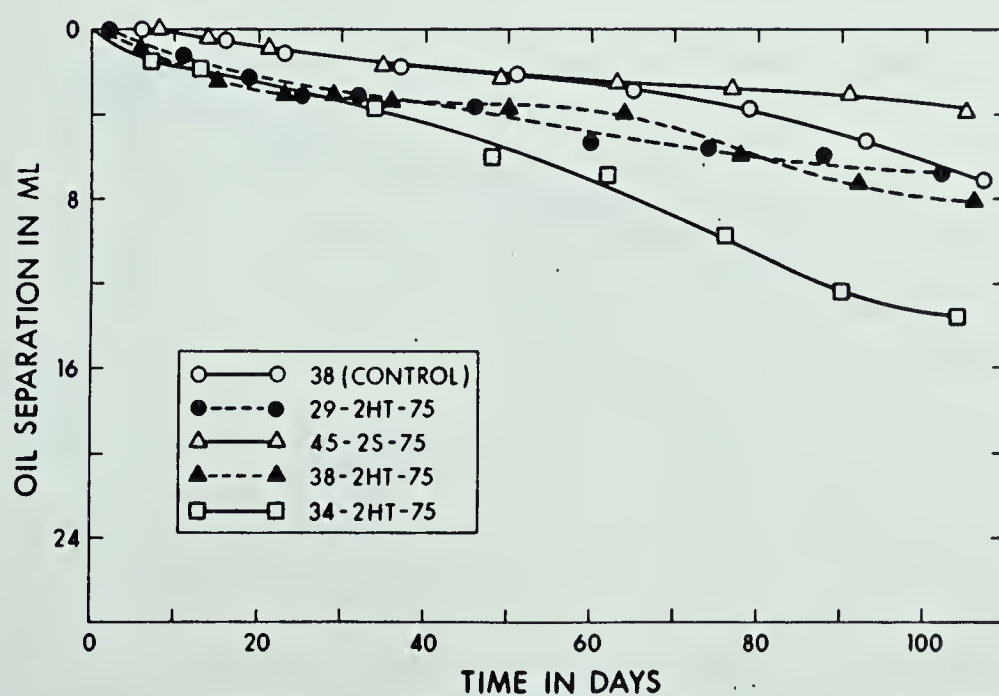


Fig. 11. Stability of Bentone Lotion Bases with Liquified Phenol.

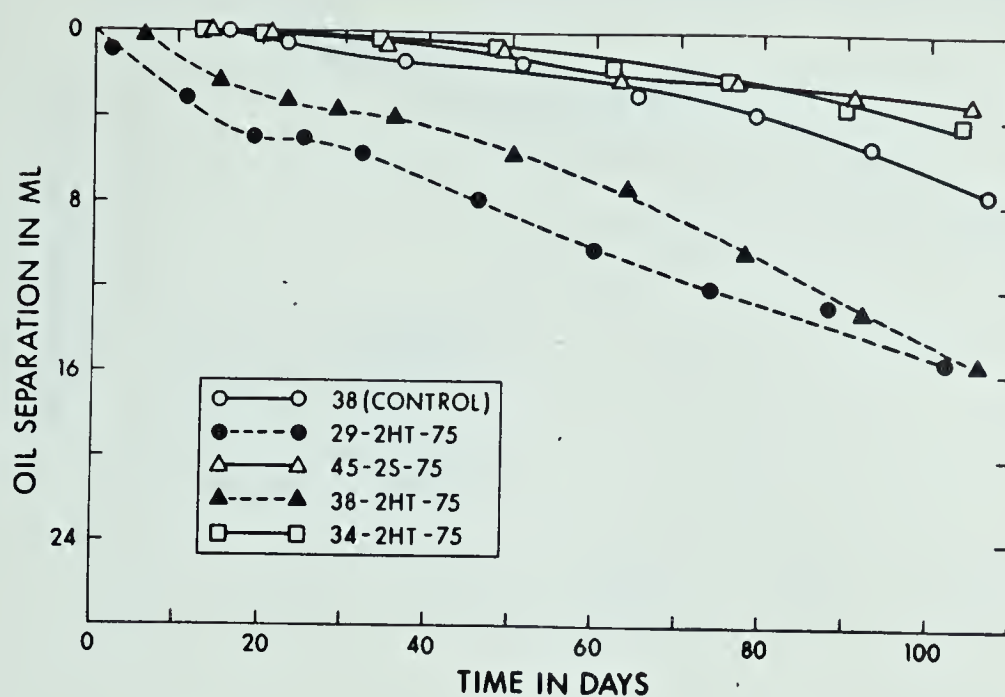


Fig. 12. Stability of Bentone Lotion Bases with Sulfur.

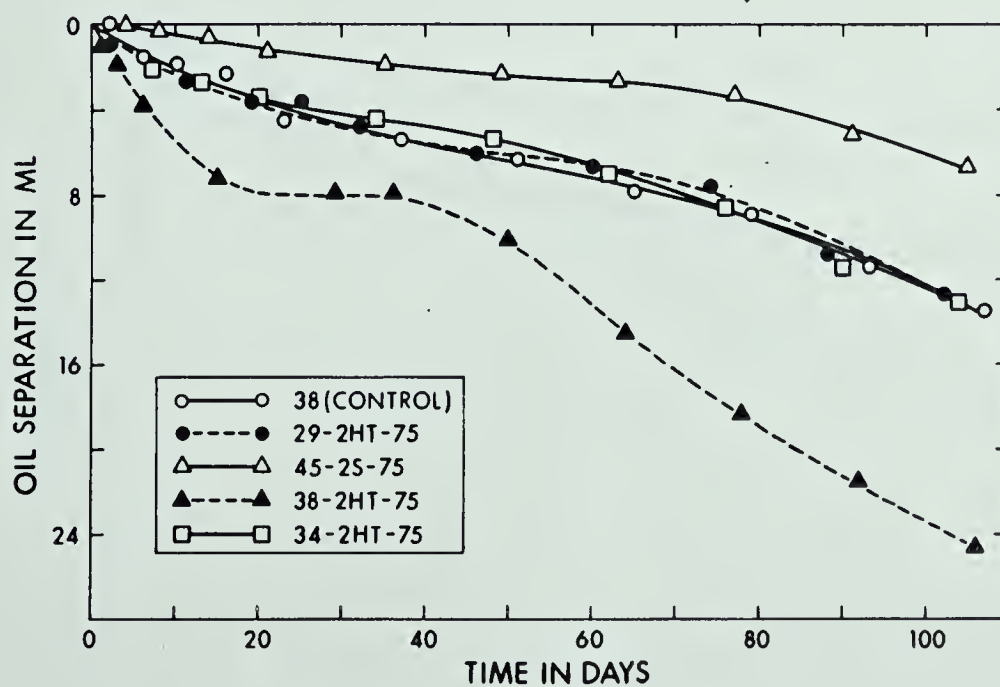


Fig. 13. Stability of Bentone Lotion Bases with Zinc Oxide.

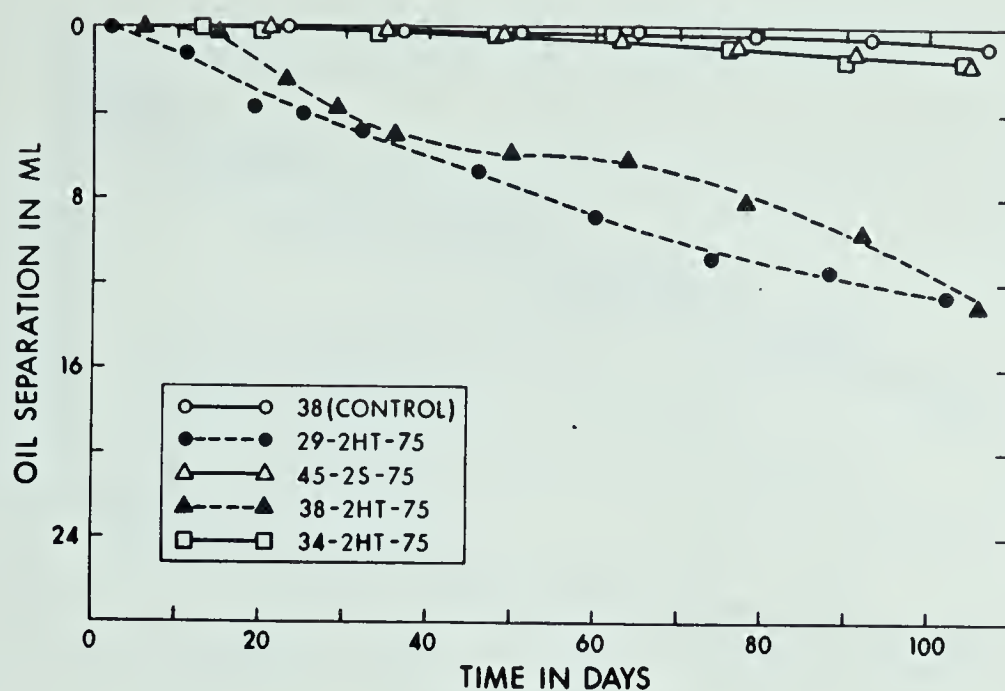


Fig. 14. Stability of Bentone Lotion Bases with Burow's Solution.

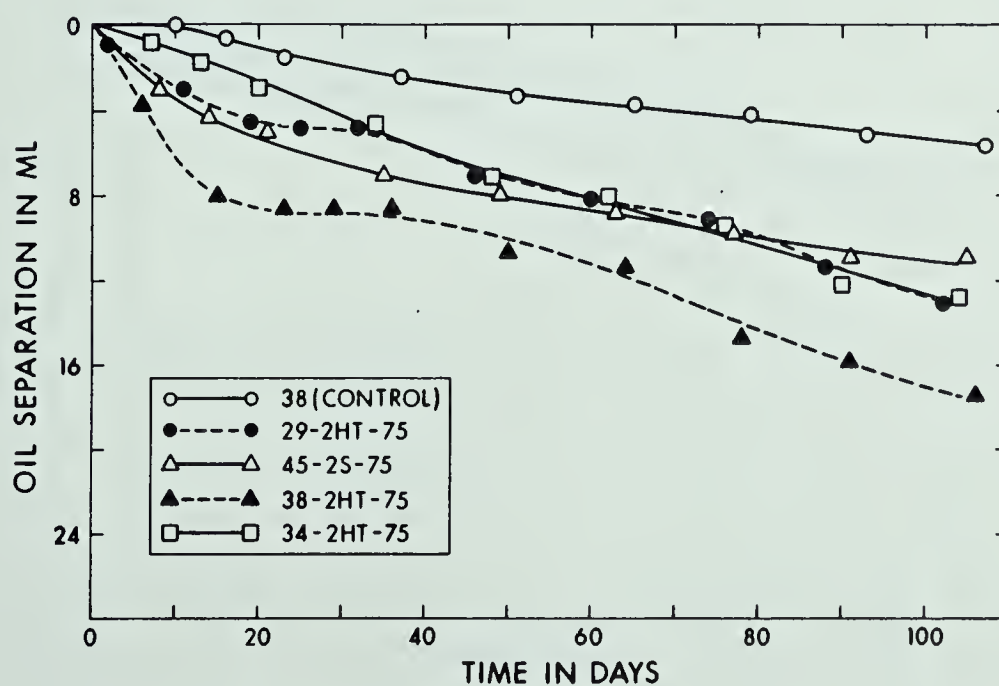


Fig. 15. Stability of Bentone Lotion Bases with Lead Subacetate Solution.

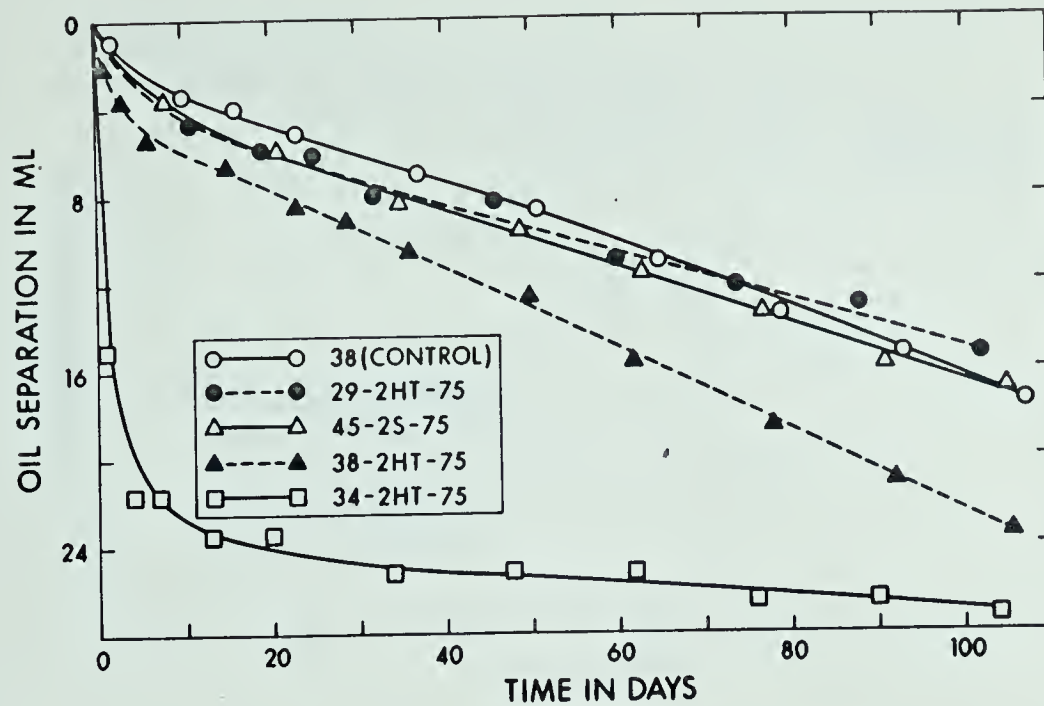


Fig. 16. Stability of Bentone Lotion Bases with Calamine.

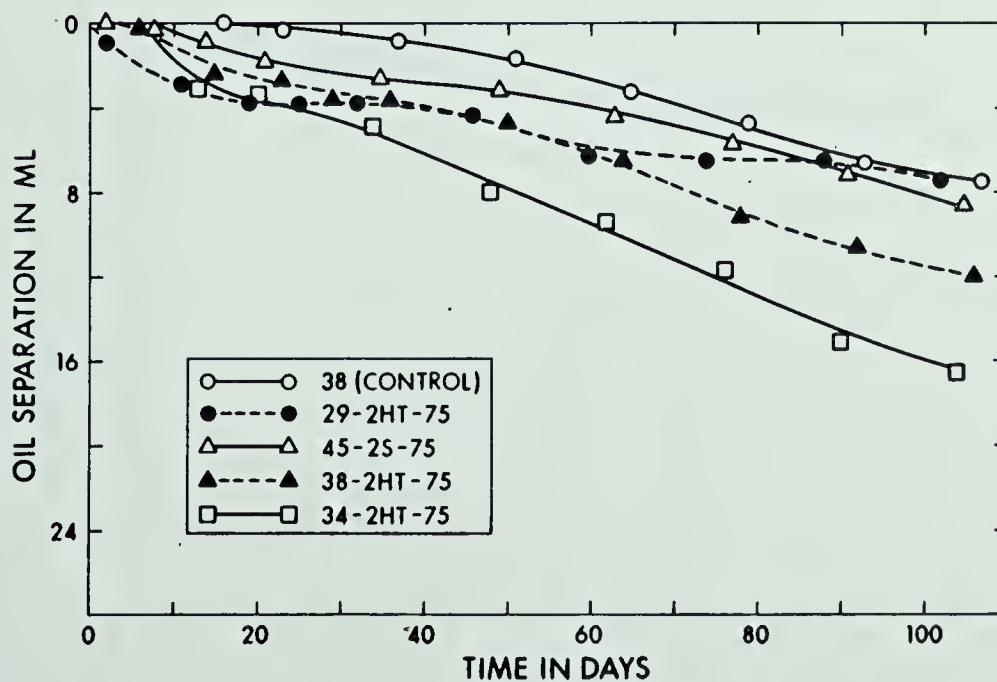


Fig. 17. Stability of Bentone Lotion Bases with Benzocaine.

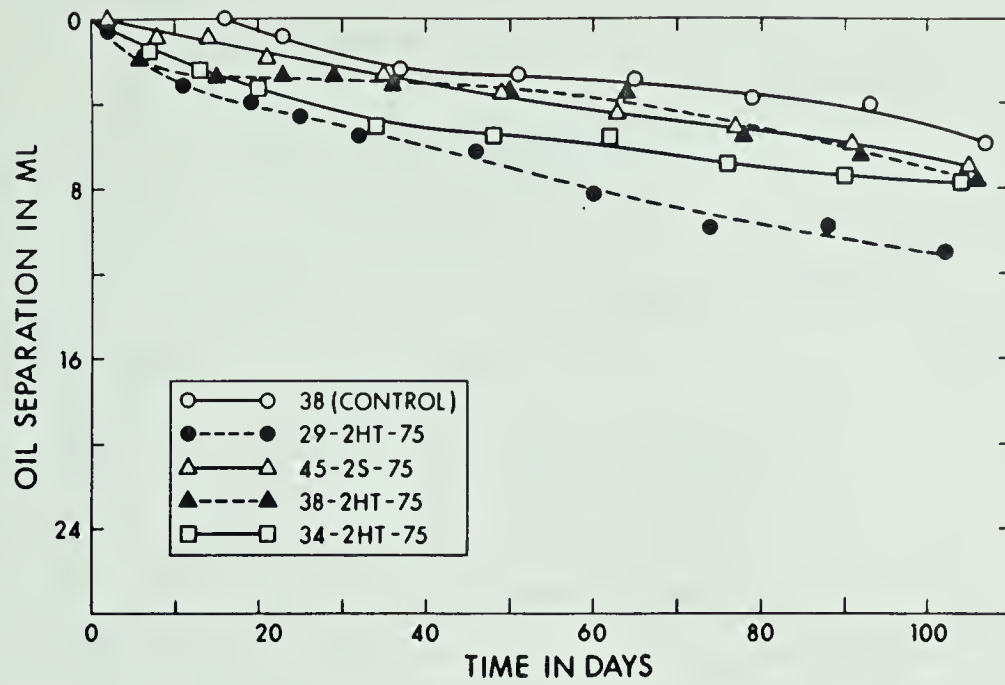


Fig. 18. Stability of Bentone Lotion Bases with Resorcinol.

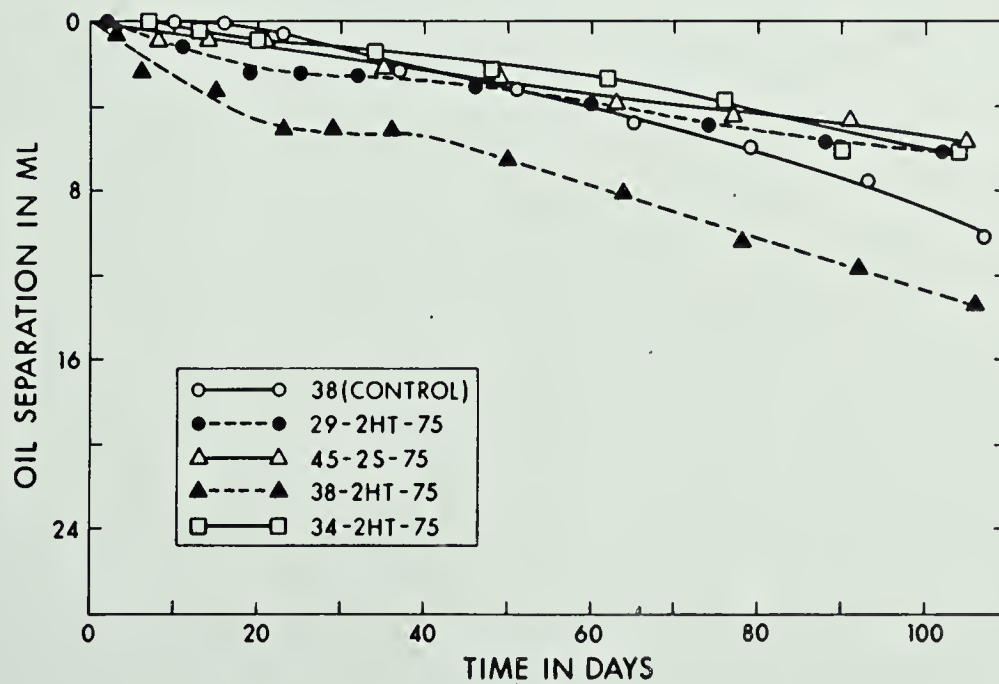


Fig. 19. Stability of Bentone Lotion Bases with Coal Tar Solution.

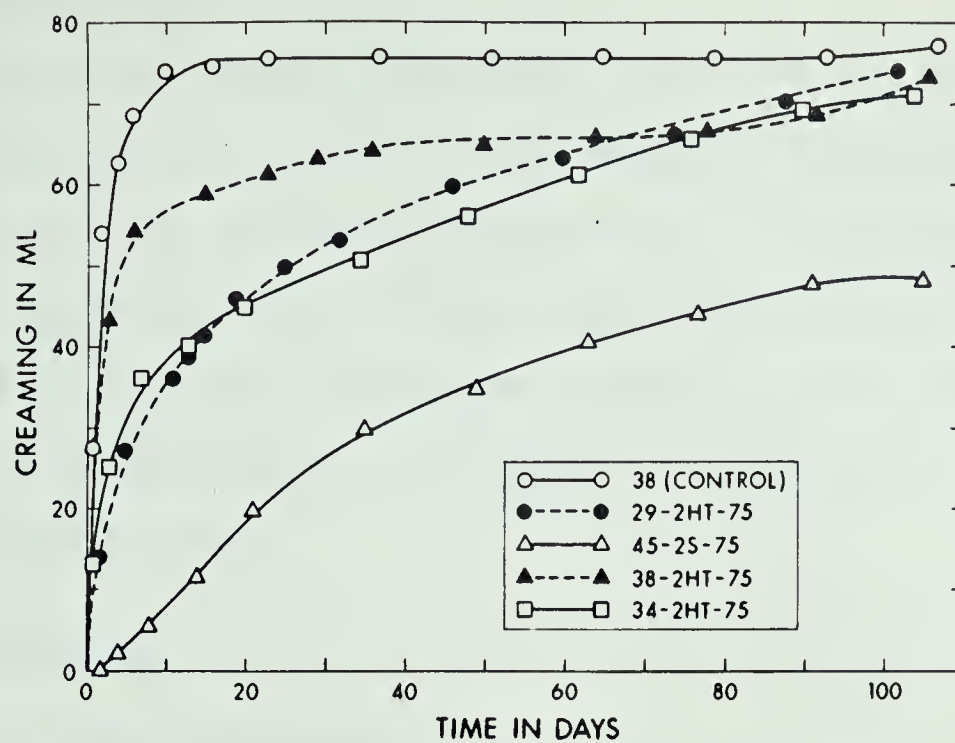


Fig. 20. Stability of Bentone Lotion Bases in Compound Menthol Formula.

BENTONE OINTMENT BASES

Two types of bases were prepared for study in this series:

1) anhydrous and 2) emulsified. The anhydrous type was formulated with Marcol 70, bentone and alcohol. In addition to these ingredients the emulsified products contained distilled water and Span 85. For each type of base the optimum concentration of each ingredient was determined on the basis of exploratory trials and aesthetic acceptability.

A. Anhydrous Bases

a) Formulation and Procedure

Marcol 70 and bentone were mixed for five minutes at high shear in a Homo-Mixer. Alcohol was then added and agitation was continued until a thick gel was formed. When gelation had progressed to a point where the instrument was no longer able to circulate the material, the base was transferred to a Waring Blendor for further mixing at the highest speed until a uniform ointment-like consistency was achieved.

In this manner, a number of batches of ointment base were prepared in triplicate from each of the bentones carried. Concentration of the ingredients was varied in order to determine the most acceptable product.

Consistency of each base was determined using a Cone Penetrometer*. A 400 g. quantity of base was packed into a stainless

* Precision Universal Penetrometer (ASTM-D217). Supplied by Lab Line Instruments, Inc., Chicago, Ill., U. S. A.

steel cup** and the surface was carefully leveled with a straight edge. The cone (without load) was adjusted to just touch the surface of the sample. It was then released for a free drop into the sample over a five second period. Readings were taken at room temperature and were recorded in 0.1 mm. of penetration.

Composition of bases prepared, together with Penetrometer readings are presented in Table XVIII.

In preparing the anhydrous bases for evaluation, it was originally intended that the formulation as employed by Billups (97), would be used throughout the series. However, with the equipment available it was found that a somewhat greater amount of bentone was required to obtain a base of satisfactory consistency.

To keep the composition uniform whenever possible for comparison purposes, and to obtain the maximum gelling for each bentone, the following ratio of ingredients was selected for use in the subsequent shelf testing procedure:

	<u>Ratio in Weight</u>		
	Marcol 70, bentone, alcohol		
Bentone 38	90	8	2
29-2HT-75	90	8	2
34-2HT-75	91	8	1
38-2HT-75	85	12	3
45-2S-75	90	8	2

Each of the selected bases as listed above was considered to be quite satisfactory. Color ranged from pale yellow for the Bentone 38 product to a dark brown for bentone 45-2S-75. All possessed good consistency with excellent spreadability.

** Cup dimensions: diameter 10 cm., height 6 cm.

TABLE XVIII

COMPOSITION AND PENETROMETER READINGS OF
ANHYDROUS OINTMENT BASES

Base	Composition, ^a % w/w			Penetrometer reading, 0.1mm.			
	Oil	Bentone	Alcohol	1	2	3	Average
Bentone 38 (Control)	91.0	6.0	3.0	413	417	407	412
	89.5	8.0	2.5	368	366	368	367
	<u>90.0</u>	<u>8.0</u>	<u>2.0</u>	365	350	353	356
	90.5	8.0	1.5	560	553	540	551
29-2HT-75	<u>90.0</u>	<u>8.0</u>	<u>2.0</u>	381	379	368	376
34-2HT-75	90.0	8.0	2.0	too thin to read			
	90.5	8.0	1.5	too thin to read			
	90.8	8.0	1.2	374	378	373	375
	<u>91.0</u>	<u>8.0</u>	<u>1.0</u>	360	358	354	357
	91.1	8.0	0.9	381	371	376	376
	91.2	8.0	0.8	396	394	401	397
38-2HT-75	90.0	8.0	2.0	too thin to read			
	88.0	10.0	2.0	442	439	447	443
	86.0	12.0	2.0	387	379	384	383
	85.5	12.0	2.5	330	337	336	334
	<u>85.0</u>	<u>12.0</u>	<u>3.0</u>	321	325	318	321
	84.5	12.0	3.5	475	460	460	465
45-2S-75	88.0	8.0	4.0	366	359	355	360
	89.0	8.0	3.0	320	325	314	320
	89.5	8.0	2.5	314	317	308	313
	<u>90.0</u>	<u>8.0</u>	<u>2.0</u>	316	313	308	312
	90.5	8.0	1.5	357	362	355	358

a Underlined values represent composition of the bases selected for use in the subsequent shelf testing procedure. Each base was prepared in triplicate.

b) Compatibility

In order to determine the utility of the prepared bases, a number of ointment formulas was selected. In each of these preparations, the required base was replaced by an equal amount of bentone base. In each case, formulation procedure either followed official directions, or consisted of instructions as indicated.

The finished ointments, in duplicate, were packaged in four ounce wide mouth glass jars sealed with a metal screw cap. Storage was at room temperature, and observations were carried out over a period of sixty days.

Index of Selected Ointment Formulas

1. Coal Tar Ointment, U.S.P.XVII (Formula A)

2. Coal Tar Ointment--Formula B

Crude Coal Tar	5.5 g.
Zinc Oxide (sifted)	5.5 g.
Corn Starch (sifted)	44.5 g.
Bentone Base, Anhydrous	<u>44.5 g.</u>
To Make -	100 g.

Procedure--The coal tar, zinc oxide and starch were levigated on a glass slab until a thick black mass was obtained. This was then incorporated into the bentone bases with further levigation until a uniform but coarse grained product was obtained. The ointment was then passed through a triple roller ointment mill to yield a smooth, thin, almost black preparation.

3. Ammoniated Mercury Ointment, U.S.P.XVII

4. Calamine Ointment, B.P.C. 1963*

* British Pharmaceutical Codex, 1963, The Pharmaceutical Press, London, England.

5. Tannic Acid Ointment

Tannic Acid	20 g.
Bentone Base, Anhydrous	<u>80 g.</u>
To Make - 100 g.	

Procedure--The tannic acid was incorporated directly into the bentone base with levigation, yielding a very grainy, coarse product. Passage through a triple roller ointment mill* gave some improvement in appearance.

6. Compound Benzoic Acid Ointment, B.P.C. 1963.

With the possible exception of the tannic acid ointments and the coal tar (Formula B) ointments, all of the preparations were of acceptable texture when first compounded. The bentone bases themselves remained virtually unchanged throughout the shelf testing procedure. However, some changes occurred in the medicated samples during this period. These changes are tabulated in Table XIX.

After two days, a progressive color change was noted in the compound benzoic acid ointments. Similarly a gradual darkening of two of the tannic acid ointments was observed after one month of testing. The development of a definite pink color in the compound benzoic acid ointments and the darkening of the tannic acid samples were found only among the ointments prepared from bentones synthesized earlier. The ointments using a base formed from Bentone 38 were free from this undesirable effect. Since it was known that each of the original clays involved in the preparation of these bentones contained variable amounts of iron

* Pascall, The Pascall Engineering Co., Ltd., England
Model 1.

TABLE XIX

SHELF TEST OF ANHYDROUS BENTONE OINTMENTS AT ROOM TEMPERATURE

Ointment Base	Property	Drugs Incorporated									
		Blank	Coal Tar Formula A	Coal Tar Formula B	Ammoniated Mercury	Calamine	Tannic Acid a	Cpd. Benzoic Acid b			
Bentone 38 (Control)	S	10 → 10	10 → 10	10 → 10	10 8	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	9 9
	C	10 → 10	8 ^s → 8 ^s	9 ^t → 9 ^t	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10
29-2HT-75	S	10 → 10	10 → 10	10 8 7	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10
	C	10 → 10	9 ^s → 9 ^s	7 ^t 6 ^t 6 ^t	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	9 ^t → 9 ^t
34-2HT-75	S	10 → 10	10 8 8	10 8 7	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10
	C	10 → 10	4 ^t → 4 ^t	4 ^t 5 ^t 5 ^t	10 9 ^s 9 ^s	10 → 10	10 → 10	9 ^s → 9 ^s	10 → 10	9 ^t → 9 ^t	9 ^t → 9 ^t
38-2HT-75	S	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10
	C	10 → 10	8 ^s → 8 ^s	10 9 ^s 9 ^s	10 → 10	10 → 10	10 → 10	9 ^s → 9 ^s	10 → 10	9 ^s → 9 ^s	10 9 ^s 9 ^s
45-2S-75	S	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10	10 → 10
	C	10 → 10	9 ^s → 9 ^s	8 ^t 9 ^t 10	10 → 10	10 → 10	10 → 10	9 ^s → 9 ^s	10 → 10	9 ^s → 9 ^s	10 → 10
Time in Days		0 30 60	0 30 60	0 30 60	0 30 60	0 30 60	0 30 60	0 30 60	0 30 60	0 30 60	0 30 60

a. After 30 days, darkening was observed in the 29-2HT-75 and 38-2HT-75 ointments.

b. After two days, pink color was developed in all the ointments except the control. The deepest color was observed in ointments 29-2HT-75 and 38-2HT-75.

S: Separation, 10=no separation, 9=trace bleeding, 8=bleeding, 7-3=increasing separation, 0=cracked.

C: Consistency, s=stiff, t=thin, 10=satisfactory.

oxide as a contaminant, it was felt that the color change could be attributed to a chemical reaction involving this element.

B. Emulsified Bases

a) Formulation and Procedure

Marcol 70 and bentone were mixed together for 10 minutes. A thin, gritty suspension was produced that changed to a thick homogeneous paste when alcohol was added. After five minutes of stirring, Span 85 was added and the mixture became somewhat thinner under continued stirring. Distilled water was then added and agitation was continued for 15 minutes. A white to very light brown ointment base was produced.

Using this procedure, a number of batches of ointment base were prepared in triplicate from each of the bentones under test. Concentration of the ingredients was varied to allow choice of the most acceptable product.

Consistency of each base was determined as before using a Cone Penetrometer. Readings were taken at room temperature and recorded in 0.1 mm. of penetration.

Composition of bases prepared, together with Penetrometer readings are presented in Table XX. Selection of the bases was made after considering consistency and other factors such as slip and spreadability on the skin.

TABLE XX

COMPOSITION AND PENETROMETER READINGS OF EMULSIFIED OINTMENT BASES

	Composition ^a , % w/w			Penetrometer reading, 0.1 mm.		
	Oil	Bentone	Alcohol	Span	85 Water	Average
Bentone 38 (control)	<u>50.0</u> 50.0	<u>6.0</u> 6.0	<u>3.0</u> 3.0	<u>3.0</u> 1.5	<u>38.0</u> 39.5	320 269
29-2HT-75	<u>50.0</u>	<u>6.0</u>	<u>3.0</u>	<u>1.5</u>	<u>39.5</u>	285
34-2HT-75	<u>50.0</u> 50.0 <u>50.0</u>	<u>6.0</u> 6.0 <u>6.0</u>	<u>3.0</u> 1.5 <u>3.0</u>	<u>1.5</u> 1.5 <u>2.0</u>	<u>39.5</u> 41.0 <u>39.0</u>	251 288 311
38-2HT-75	<u>50.0</u> 50.0 50.0	<u>6.0</u> 6.0 6.0	<u>3.0</u> 3.0 2.0	<u>1.5</u> 2.0 1.5	<u>39.5</u> 39.0 40.5	364 389
45-2S-75	<u>50.0</u> 50.0 <u>50.0</u>	<u>6.0</u> 6.0 <u>6.0</u>	<u>3.0</u> 3.0 <u>3.0</u>	<u>3.0</u> 2.0 <u>1.5</u>	<u>38.0</u> 39.0 <u>39.5</u>	265 232

a Underlined values represent composition of the bases selected for use in the subsequent shelf testing procedure. Each base was prepared in triplicate.

Formulations chosen for use in the subsequent shelf testing procedure were:

	Ratio in Weight				
	Marcol 70,	Bentone,	Alcohol,	Span 85,	Water
Bentone 38	50	6	3	3	38
29-2HT-75	50	6	3	1.5	39.5
34-2HT-75	50	6	3	2	39
38-2HT-75	50	6	3	1.5	39.5
45-2S-75	50	6	3	2	39

In each case the bases chosen were considered to be of better than acceptable quality and thus suitable for use as medicament carriers.

b) Compatability

As explained previously for the anhydrous bases, a number of ointment formulas were selected to determine the utility of the emulsified bases. In each case the recommended or usual vehicle was replaced with an equal amount of emulsified bentone base, and formulation procedure either followed official directions or consisted of instructions as indicated. Each formula was prepared in duplicate.

The finished preparations were stored in four ounce glass ointment jars with metal screw caps. Observations were carried out at room temperature over a period of 45 days. Results are tabulated in Table XXI.

Index of Selected Ointment Formulas

1. Calamine Ointment, B.P.C. 1963.
2. Ichthammol Ointment, B.P.C. 1963.
3. Salicylic Acid Ointment, B.P. 1963

4. Burow's solution Ointment

Burow's Solution	20 g.
Lanolin, anhydrous	40 g.
Bentone base, emulsified	<u>40 g.</u>
To Make -	100 g

Procedure--The Burow's solution was taken up in the lanolin by mixing on an ointment slab. This resulting mixture was then rubbed up with the bentone base.

5. Tannic Acid Ointment

Tannic Acid	20 g.
Bentone Base, emulsified	<u>80 g.</u>
To Make -	100 g.

Procedure--The tannic acid was dispersed through the base by mixing on an ointment slab. After passage through a triple roller ointment mill, an acceptable product was obtained. However, after standing for one week, the preparation was found to have separated badly.

6. Liquified Phenol Ointment

Liq. Phenol	2 g.
Bentone Base, emulsified	<u>98 g.</u>
To Make -	100 g.

Procedure--The two ingredients were mixed together on an ointment slab. A very thin preparation resulted.

7. Sulfur Ointment, B.P. 1963

8. Coal Tar Ointment

Coal Tar Solution	10 g.
Bentone Base, emulsified	<u>90 g.</u>
To Make -	100 g.

Procedure--Prepared by simple mixing.

With the exception of ointments of ichthammol, tannic acid and phenol, all the ointments had acceptable consistency. Color changes were also observed in salicylic acid and tannic acid ointments as noted previously among the anhydrous ointments. However, the color development in this series was more pronounced.

TABLE XXI
SHELF TEST OF EMULSIFIED BENTONE OINTMENTS AT ROOM TEMPERATURE

Ointment Base	Property	Drugs Incorporated					
		Blank	Calamine	Ichthammol	Burow's Solution	Salicylic Acid ^a	
Bentone 38	S	10	10	5 0 0 0	10	10	10
(Control)	C	10	10	8 ^t 9 ^t 9 ^t 9 ^t	10	10	9 ^s 8 ^s 5 ^s
29-2HT-75	S	10	10	7 0 0 0	10	10	10
	C	10	10	6 ^t — 6 ^t —	10	10	10 10 8 ^s 8 ^s
34-2HT-75	S	10	10	7 0 0 0	10	10	10
	C	10	10	5 ^t — 5 ^t —	10	10	10
38-2HT-75	S	10	10	8 3 3 3	10	10	10
	C	9 ^t — 9 ^t —	10	6 ^t — 6 ^t —	8 ^t —	8 ^t —	8 ^t
45-2S-75	S	10	10	6 0 0 0	10	10	10
	C	10	10	8 ^t — 8 ^t —	10	10	8 ^s 8 ^s 8 ^s
Time in Days		0 7 21 45	0 7 21 45	0 7 21 45	0 7 21 45	0 7 21 45	0 7 21 45

(Continued)

Ointment Base	Property	Drugs Incorporated					Sulfur Ppt.	Coal Tar Solution		
		Tannic Acid	Liquified Phenol							
Bentone 38	S	10 0 0 0	10 10 9 8				10	10	10 9 9 8	
(Control)	C	6 ^s 8 ^s 8 ^s 8 ^s	3 ^t 6 ^t 7 ^t 7 ^t				10	10	10 9 ^s 8 ^s 8 ^s	
29-2HT-75	S	10 0 0 0	10 9 8 8				10	10	10 8 7 7	
	C	7 ^s 9 ^s 9 ^s 9 ^s	5 ^t 5 ^t				10	10	10 10	
34-2HT-75	S	10 0 0 0	10 9 8 7				10	10	10 9 7 7	
	C	5 ^s 5 ^s 5 ^s 3 ^t	3 ^t 3 ^t				10	10	10 10	
38-2HT-75	S	10 0 0 0	10 9 8 8				10	10	10 10 8 7	
	C	6 ^s 6 ^s 6 ^s 4 ^t	4 ^t 4 ^t				10	10	10 10	
45-2S-75	S	10 0 0 0	10 9 8 8				10	10	10 10 8 8	
	C	7 ^s 7 ^s 7 ^s 5 ^t	5 ^t 5 ^t				10	10	10 10	
Time in Days		0 7 21 45	0 7 21 45	0 7 21 45	0 7 21 45	0 7 21 45	0 7 21 45	0 7 21 45	0 7 21 45	

- a. Pink color developed gradually among all ointments except those made with Bentone 38. At the end of test period, the degree of coloration: 45-2S-75<34-2HT-75<29-2HT-75=38-2HT-75.
- b. Darkening was observed among all the ointments. An immediate coloration was noted in ointments 29-2HT-75 and 38-2HT-75; for others it occurred gradually after three days. At the end of the test period, the degree of darkening: 38<45-2S-75=34-2HT-75<29-2HT-75=38-2HT-75.
- S: Separation; 10=no separation, 9=trace bleeding, 8=bleeding, 7-3=increasing separation, 0=cracked.
- C: Consistency; s=stiff, t=thin; 10=satisfactory.

DISCUSSION AND SUMMARY

Ten native bentonites representative of known deposits within the Province of Alberta were collected, purified by water sedimentation and subjected to limit tests as detailed in the B. P. 1963 monograph. From the results obtained, and from consideration of the commercial availability and geographical locations, four samples were chosen to undergo adsorptive exchange reaction with selected quaternary ammonium salts (Arquads 2HT-75 and 2S-75). In addition to these Alberta clays, a high grade bentonite from South Dakota was employed as the bentonite control.

The replacement of exchangeable ions which were originally held on the montmorillonite lamellae for large organic cations was observed to be an instantaneous reaction. The highly-peptized clay-water system was completely flocculated by the addition of the hot Arquad dispersion. The dried reaction product, (bentone), was no longer hydrophilic and it possessed remarkable gelling characteristics in mineral oil-alcohol binary media. These organo-clays yielded dispersions, which had much greater consistency than corresponding magmas prepared with the untreated counterparts.

Based on the consistency data obtained for the ten synthesized bentones, and the pharmaceutical acceptability of the products, four bentones were chosen for further evaluation to measure their utility in forming lotion and ointment bases. One commercial product, Bentone 38, was included in this study as the bentone control.

For preliminary screening purposes, 100 meq. of Arquad per

100 grams of purified clay was used for the complexation. This amount of Arquad was considered to be sufficient to cover all the exchange positions on the clay surface, thus yielding a bentone of maximum gelling ability. However, it was found later that the optimum Arquad-bentonite ratio was somewhat less than the quantity employed here.

A series of tests was carried out to determine the proper ratio for complexation. Since minor variation in the coverage of clay surface by organic material had a large influence upon the rheological properties of the resulting products, difficulties were encountered in getting reproducible data. In addition, the non-uniformity of the Arquads employed made the situation more complicated. However, by adjusting the amount of Arquad, prior to the filtration of reaction product, reproducible batches of bentone could be obtained.

As indicated by the consistency curves taken for both bentonite magmas and corresponding bentone dispersions, no relationship could be shown between the dispersion consistencies of the untreated bentonites and the corresponding bentones.

The effects of chemical and mechanical energy on the gel strength of bentone dispersions were demonstrated for Bentone 38 and bentone 45-2S-75. The addition of minor amounts of polar additive greatly enhanced the solvation of bentone in the highly non-polar organic medium. Fifty per cent of alcohol based on the weight of bentone employed was shown to be the optimum concentration. As for the mechanical energy applied in preparing the gels, in the range tested, there was found to be an increase

in viscosity of the dispersion with increase in shear rate.

Efforts were made to use differential thermal analysis and x-ray diffraction data to characterize the prepared bentones. Because of a lack of sensitivity of the differential thermal apparatus, satisfactory curves could not be obtained, although in some cases, low grade but characteristic peaks were observed. It was felt, however, that this method would be valuable for identification of the organo-bentonites provided a more sophisticated instrument were employed. X-ray diffraction data for each of the bentones were obtained, and these were presented in table form as a matter of interest only. Since identification of the bentones would require both differential thermal analysis and x-ray data, analysis of the latter results was not attempted.

Emulsified lotion bases were prepared from each of the five bentones. The commonly used dermatological medicaments, calomel, boric acid, phenol, sulfur, zinc oxide, Burow's solution, lead subacetate solution, calamine, benzocaine, resorcinol, coal tar solution and menthol compound, were incorporated into the vehicles, and shelf testing at room temperature was performed. From the over-all results obtained, bentone lotion bases were thought to be excellent vehicles for these drugs. With one exception, no incompatibilities were observed in the medicated lotions. The calamine lotion, B. P. 1963, however, appeared to promote a phase inversion of the emulsion base formed with bentone 34-2HT-75. For that reason, this base was considered to be unsuitable for use with this medicament formula. Bentone 45-2S-75 showed to be as good as or even slightly superior to

the control. Bentones 29-2HT-75 and 38-2HT-75 appeared to possess inferior emulsifying ability which could not be related to the gelling capacity of the bentones.

It was observed that Burow's solution had a stabilizing effect on the emulsified bentone lotion bases. This was in agreement with the observation made on bentonite magmas by Nash (35) who proposed that in a certain pH range, aluminum ions acted as strong bonding agents between clay particles.

Lead ions seemed to accelerate the separation of oil phase from the lotion bases. Lotions with a heavy load of powdered ingredient were shown to be more unstable than the blank. It was noted that the addition of both phenol and resorcinol to the bentone bases had unpredictable effects on the stability of the resulting lotions. This was attributed to the adsorption of large amounts of phenol by the quaternary ammonium-treated clays as reported by Roberts et al. (98), which caused changes in the structure of the organo-clay. These changes were evidenced by increased or decreased stability of the system.

Highly acceptable and stable anhydrous and emulsified ointment bases were obtained using bentone as the gelling or emulsifying agents. While the anhydrous bases ranged in color from light brown to an olive shade, these bases possessed excellent spreadability when applied to the skin. The consistency of the bases could be adjusted by varying the amount of bentone employed. No heating or cooling process was necessary for preparing these bases. However, an instrument which could exert high shear should be used for manufacturing such ointment bases.

Selected drugs were incorporated into the bases. and shelf testing was carried out at room temperature over a period of 45 and 60 days. In most cases, a progressive darkening in color was observed in the tannic acid ointments; and for the salicylic acid and the compound benzoic acid products, a gradually deepening pink color was noted. These effects were attributed to the presence of iron as an impurity in the original clays. The removal of this contaminant was thought to be necessary if these bases were to be used as carriers for these two compounds or any other substances known to react with iron.

In general, the anhydrous bentone ointment bases were satisfactory as vehicles for calamine, ammoniated mercury and crude coal tar. However, an incompatibility appeared to be present between crude coal tar and bentone 34-2HT-75, since the resulting product was too thin to be a good ointment.

The emulsified ointment bases were excellent as vehicles for calamine, Burow's solution, sulfur and coal tar solution. Ichthammol, tannic acid and phenol were incompatible with these bentone bases. The latter preparations were very thin or separated or even cracked after storage for one week.

CONCLUSIONS

1. Pharmaceutical acceptable bentones can be prepared from Alberta bentonites by a relatively simple reaction with commercially available quaternary ammonium compounds.
2. Measurable differences in physical characteristics exist among bentones prepared from bentonites taken from different deposits. For this reason certain of the bentones appear to be more suitable than others in the formulation of lotion and/or ointment bases.
3. From a study of rheograms plotted for magmas of the purified clays and for oil dispersions of the corresponding bentones, it is evident that relative consistency characteristics of the individual clays are not carried forward in the same order of magnitude to the corresponding bentones.
4. Emulsion type lotion bases prepared from the synthesized bentones, mineral oil and water yield a useful w/o vehicle with excellent stability and compatibility.
5. Ointment bases, both anhydrous and emulsified, when prepared from these bentones and mineral oil and/or water, have a good range of compatibility and excellent spreadability. However, traces of iron salts in the purified clays are thought to be responsible for the development of color in some medicated ointments. The removal of this contaminant prior to synthesis of the bentones should greatly increase the utility of such bases, allowing the preparation of tannic and salicylic acid ointments without fear of color development.

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APPENDIX

Notations

- a. Values in all Tables represent two determinations on two different samples.
- b. For each sample, the up-curve deflections are listed in the top line reading from left to right in ascending order. The down-curve deflections are listed in the bottom line reading from right to left in descending order.
- c. Time interval between readings was 15 seconds.
- d. All readings were taken at 30°C.

TABLE I

DIAL DEFLECTION READINGS FOR 5 PER CENT W/W BENTONITE MAGMAS

Bentonite Sample	Dial Deflection a, b, c, d									
	3 r.p.m.	6 r.p.m.	11 r.p.m.	22 r.p.m.	33 r.p.m.	67 r.p.m.	100 r.p.m.	200 r.p.m.	300 r.p.m.	
29 (control)	23	28	32	37	43	57	71	103	130	
	9	10	17	22	28	43	59	96		
	20	27	33	45	51	67	76	108	137	
	10	13	18	23	30	46	62	102		
34	60	74	100	133	158	217	260			
	60	72	99	129	158	214				
	55	70	89	120	140	192	234			
	55	69	91	116	140	189				
38	2	3	4	6	7	12	18	33	46	
	3	4	6	7	11	14	20	34		
	2	3	4	5	6	11	16	30	42	
	2	4	6	7	10	13	18	32		
45	10	17	25	41	57	89	118	188	250	
	15	19	31	43	57	88	118	188		
	13	22	32	51	66	103	135	213	278	
	17	22	35	51	65	101	134	211		

TABLE II

EFFECT OF ALCOHOL ON GEL STRENGTH OF BENTONE 38 DISPERSIONS

% w/w of Alcohol	Dial Deflection a, b, c, d									
	3 r.p.m.	6 r.p.m.	11 r.p.m.	22 r.p.m.	33 r.p.m.	67 r.p.m.	100 r.p.m.	200 r.p.m.	300 r.p.m.	
0	2	4	5	9	15	30	43	87	118	
	3	5	9	13	17	29	42	81		
	2	2	5	9	15	28	43	85	120	
	4	5	9	12	16	28	43	80		
0.5	13	14	22	24	33	53	73	125	170	
	16	17	19	23	31	49	70	117		
	15	16	27	30	40	62	84	142	192	
	18	19	22	31	38	61	82	133		
1.0	128	140	174	200	225	298				
	108	120	164	194	240					
	120	132	156	181	202	270				
	98	120	152	178	215					
1.5	154	168	194	227	258					
	150	163	190	220						
	170	182	218	248	279					
	166	176	214	237						
2.0	188	200	226	270						
	200	216	232							
	175	192	220	265						
	180	200	233							

TABLE III

EFFECT OF ALCOHOL ON GEL STRENGTH OF BENTONE 45-2S-75 DISPERSIONS

% w/w of Alcohol	Dial Deflection a, b, c, d											
	3 r.p.m.	6 r.p.m.	11 r.p.m.	22 r.p.m.	33 r.p.m.	67 r.p.m.	100 r.p.m.	200 r.p.m.	300 r.p.m.			
0	2	3	5	10	16	29	44	83	122			
	3	5	9	11	17	30	43	83				
	3	3	5	10	14	28	43	83	124			
	4	5	10	12	17	29	44	83				
0.5	36	39	45	54	68	97	123	192	258			
	32	34	41	48	63	90	119	189				
	40	42	48	58	71	100	127	199	262			
	34	35	44	53	66	94	122	196				
1.0	83	86	88	99	113	155	198	300				
	74	75	81	92	113	153	194					
	80	83	91	100	115	156	197	299				
	75	76	83	93	113	152	193					
1.5	63	67	74	82	94	130	166	254				
	60	61	65	75	92	127	163					
	60	65	73	80	92	127	162	246				
	58	60	64	77	90	123	157					
2.0	57	59	64	71	85	116	148	228	298			
	51	51	57	67	80	111	142	220				
	56	57	65	72	84	115	146	224	295			
	49	51	57	67	80	110	141	218				

TABLE IV

EFFECT OF SHEAR RATE ON GEL STRENGTH OF BENTONE 38 DISPERSIONS

Powerstat Setting	Dial Deflection a, b, c, d									
	3 r.p.m.	6 r.p.m.	11 r.p.m.	22 r.p.m.	33 r.p.m.	67 r.p.m.	100 r.p.m.	200 r.p.m.	300 r.p.m.	
60	2	3	11	16	24	41	59	106	152	
	4	5	14	19	25	42	59	106		
	4	6	10	16	23	42	60	113	160	
	6	8	12	17	23	41	58	109		
70	18	19	29	35	45	69	92	154	214	
	20	20	23	31	39	62	86	141		
	20	25	37	42	55	82	110	182	246	
	20	21	28	35	47	70	96	165		
80	40	56	72	90	108	146	182	274		
	43	52	68	85	104	142	176			
	55	62	80	100	122	162	200	298		
	57	60	78	93	116	158	194			
90	99	104	120	142	165	216	281			
	76	88	116	128	160	214				
	108	120	131	160	180	238	299			
	83	96	121	152	181	238				
100	112	127	152	176	205	273				
	96	120	148	172	217					
	137	145	178	204	223	295				
	110	132	168	200	239					

TABLE V

EFFECT OF SHEAR RATE ON GEL STRENGTH OF BENTONE 45-2S-75 DISPERSIONS

Powerstat Setting	Dial Deflection a, b, c, d									
	3 r.p.m.	6 r.p.m.	11 r.p.m.	22 r.p.m.	33 r.p.m.	67 r.p.m.	100 r.p.m.	200 r.p.m.	300 r.p.m.	
60	15	18	28	35	44	64	90	148	201	
	16	17	26	34	40	62	84	143		
	13	16	24	32	42	62	82	142	193	
	14	17	24	32	39	59	80	139		
70	35	37	55	61	71	96	124	191	253	
	33	38	47	55	66	90	122	187		
	32	36	48	57	66	92	112	179	240	
	30	33	42	51	61	86	109	177		
80	48	53	72	82	91	121	152	221	286	
	44	52	64	73	84	116	145	218		
	49	52	68	75	84	114	143	212	278	
	43	49	60	68	78	107	137	210		
90	55	60	70	80	97	126	160	252		
	55	57	70	80	94	127	162			
	64	66	72	82	97	120	157	238		
	49	52	63	74	88	122	154			
100	74	78	82	93	107	145	181	285		
	70	72	77	89	107	143	176			
	90	91	98	108	121	167	215			
	78	80	87	95	119	160	212			

TABLE VI

DIAL DEFLECTION READINGS FOR 3 PER CENT W/W BENTONE DISPERSIONS

Bentone Sample	Dial Deflection a, b, c, d											
	3 r.p.m.	6 r.p.m.	11 r.p.m.	22 r.p.m.	33 r.p.m.	67 r.p.m.	100 r.p.m.	200 r.p.m.	300 r.p.m.			
38 (control)	68	76	89	112	137	185	229					
	65	71	89	110	135	185						
	60	70	82	105	125	172	214					
	63	72	84	102	126	172						
29-2HT-75	80	84	92	102	120	153	185	274				
	66	68	82	92	110	145	180					
	72	73	80	90	108	140	174	268				
	60	64	73	82	96	132	169					
34-2HT-75	34	39	49	60	72	104	134	218	291			
	34	37	45	56	67	98	129	210				
	30	33	42	54	66	96	126	206	280			
	31	33	42	52	62	92	121	199				
38-2HT-75	29	34	41	51	63	89	115	187	251			
	28	30	38	47	58	85	113	182				
	24	28	36	45	56	80	107	178	240			
	23	25	33	41	52	76	105	173				
45-28-75	69	72	80	96	110	143	178	266				
	60	62	75	86	103	139	174					
	68	70	75	89	106	141	179	277				
	65	66	75	85	102	138	175					

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